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Original Communications

DIAGNOSIS AND MANAGEMENT OF SEVERE INFECTIONS IN INFANTS AND CHILDREN: A REVIEW OF EXPERIENCES SINCE THE INTRODUCTION OF SULFONAMIDE THERAPY

I. SEPSIS OF LATERAL SINUS PHLEBITIS

ALEXIS F. HARTMANN, M.D., DOROTHY WOLFF, PH.D., AND FRANCES LOVE, M.D.
ST. LOUIS, MO.

THERE can be little doubt that many of the remarkable recoveries from infections since the introduction of sulfonamide drug therapy have been the direct results of such treatment. It is also becoming increasingly evident, however, that other factors such as early and accurate bacteriologic diagnosis, which may at an early stage of infection point clearly to the need of treatment other than chemotherapy, effective correction of serious disturbances in water and electrolyte metabolism (particularly severe dehydration and acidosis) and maintenance of adequate nutrition in the broadest sense, both of which may require much skillful intravenous administration, serum therapy, and surgical procedures, may at times be of equal or of even greater importance. Because of these facts we are convinced that never before has there been a greater need for the fullest cooperation between the pediatrician, or internist, the surgeon, and the diagnostic laboratories; without it, the potentialities of chemotherapy may be largely unrealized, and, in fact, this most valuable measure may be so misused as to be largely discredited.

Just prior to the availability of sulfonamide drugs, one of us (A. F. H.) with Cone[1] reviewed the sixty cases of phlebitis of the lateral sinus encountered in the St. Louis Children's Hospital from 1920 through 1936. We expressed ourselves as "looking forward to the effects which might be obtained by the use of 'prontosil' and 'prontylin' (sulfanilamide)" feeling "that these substances may prove to be of great value in controlling septicemia and the development of metastatic foci during the most dangerous preoperative and postoperative periods

From the Departments of Pediatrics and Otolaryngology, Washington University School of Medicine, and the St. Louis Children's Hospital.

of lateral sinus phlebitis." We wish now to report on our experiences with this serious condition over the past five years in much the same way as we did in our previous communication.

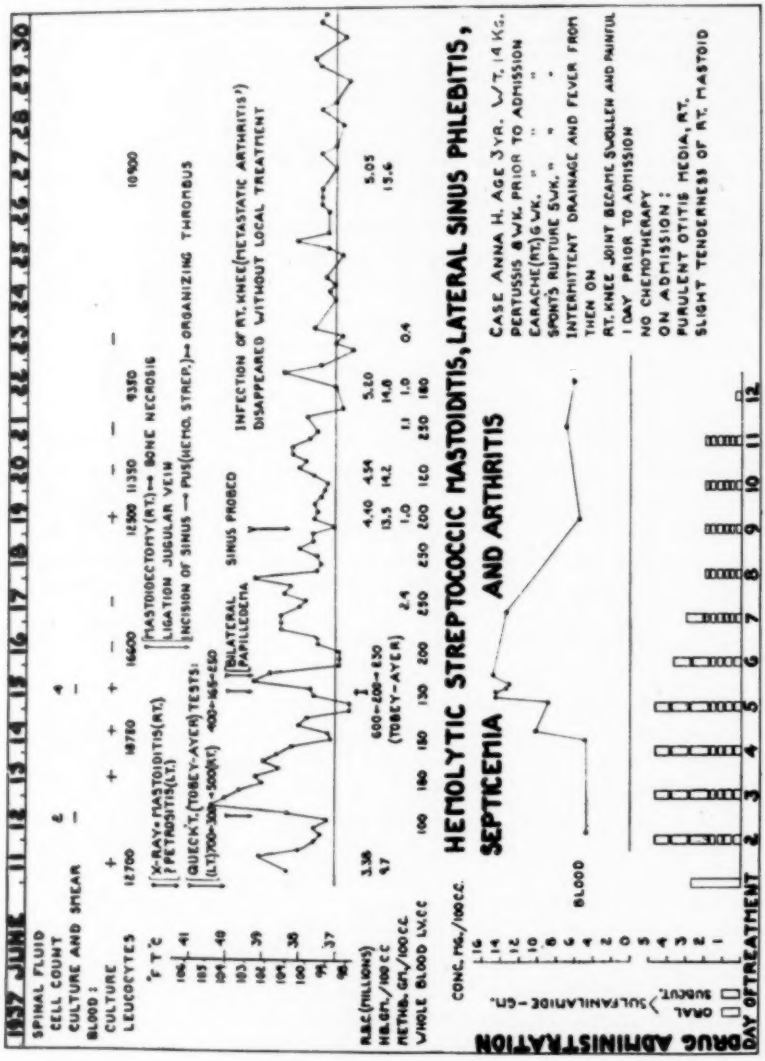


Chart 1.

REPORT OF RECOVERED CASES

CASE 1 (Chart 1 and Table I).—This 3-year-old girl, A. H., developed pertussis eight weeks prior to admission and two weeks later complained of earache on the right side. One week later there occurred spontaneous rupture of the right drum

with purulent drainage. There were then periods of intermittent drainage and high fever ranging up to 105° F., and during the week just before admission she was very irritable and vomited several times. On the day before admission the right knee became swollen and painful. No chemotherapy was given during this period.

On admission on June 11, 1937, examination revealed a freely draining right ear with obliteration of all landmarks on the drum. There was tenderness over the right mastoid and x-ray evidence of mastoiditis with breakdown of cell septa on that side. The leucocyte count was 12,700 with moderate left shift. The following morning it was thought that a thrombosed jugular vein could be palpated in the neck; however, lumbar puncture revealed a negative Tobey-Ayer test and essentially normal spinal fluid. Blood culture taken on admission was reported on this day to be positive for hemolytic streptococci. Chemotherapy with sulfanilamide orally and subcutaneously was instituted shortly after admission and was followed by a rapid improvement with fall in temperature after a sharp rise on June 12. Then again on June 15 there was high remittent fever, and at this time bilateral papilledema was noted. Blood cultures continued to be positive for hemolytic streptococci. The Tobey-Ayer test was repeated and found positive on the right side. Accordingly, on June 16 a right mastoidectomy was performed by Dr. Lee Wallace Dean, Jr., revealing bone necrosis and pus and an organizing thrombus in the lateral sinus. The jugular vein was then ligated in the neck. From the pus in the sinus hemolytic streptococci were cultured. The temperature continued to be moderately elevated and on June 19 a probe was inserted into the lateral sinus to secure better drainage, following which the blood culture again became positive after two successive negative cultures. The following day it was again negative. Recovery thereafter was uneventful, and the knee involvement disappeared without local treatment. Throughout this illness, considerable supportive treatment in the form of frequent whole blood transfusions was given. Cyanosis from methemoglobinemia which developed with intensive sulfanilamide therapy was controlled by administration of methylene blue intravenously.

CASE 2 (Chart 2 and Table I).—This 2-year-old boy, J. G., had spontaneous rupture of both eardrums following a generalized upper respiratory infection five months previously. Intermittent pain and discharge subsequently were noted. Two weeks before entry a tender swelling appeared in the neck on the left side below the mastoid, and fever and a watery diarrhea developed. On the day before entry on June 28, 1937, he complained of pain on motion of the legs. Although treated for the cervical adenitis, no chemotherapy was given prior to hospital entry.

The initial examination revealed an acutely ill child with cervical adenitis, swelling and tenderness of the right knee joint, and with intact and retracted but gray and thickened drums. There were no external signs of mastoiditis, but x-ray revealed poorly pneumatized mastoids, hazy on both sides with a tendency toward acumination on the right. Lumbar puncture the following day showed the Tobey-Ayer test to be questionably positive; on the second day following it was frankly positive on the right side. The temperature for the first few days of hospital stay was septic in type and blood cultures for the first three days were positive for hemolytic streptococci. Aspiration of the right knee joint yielded pus from which hemolytic streptococci grew. The leucocyte count on admission was 14,750 with only slight left shift. Chemotherapy was instituted with oral doses of sulfanilamide, and the knee joint was twice irrigated with a 1 per cent solution of sulfanilamide. The joint fluid was sterile after the first irrigation. The temperature showed only slight response and on July 3, the sixth day of treatment, left simple mastoidectomy was performed by Dr. Harry Lyman with exposure and incision of the lateral sinus. A coalescent type of mastoiditis was present with an organizing

clot in the sinus from which hemolytic streptococci were cultured. Just preceding the mastoidectomy the left jugular vein was ligated in the neck, and an abscess beneath the sternocleidomastoid muscle drained. The temperature remained elevated slightly for the following two weeks, but with the discontinuance of sulfanilamide on July 20, it came to normal and remained so thereafter.

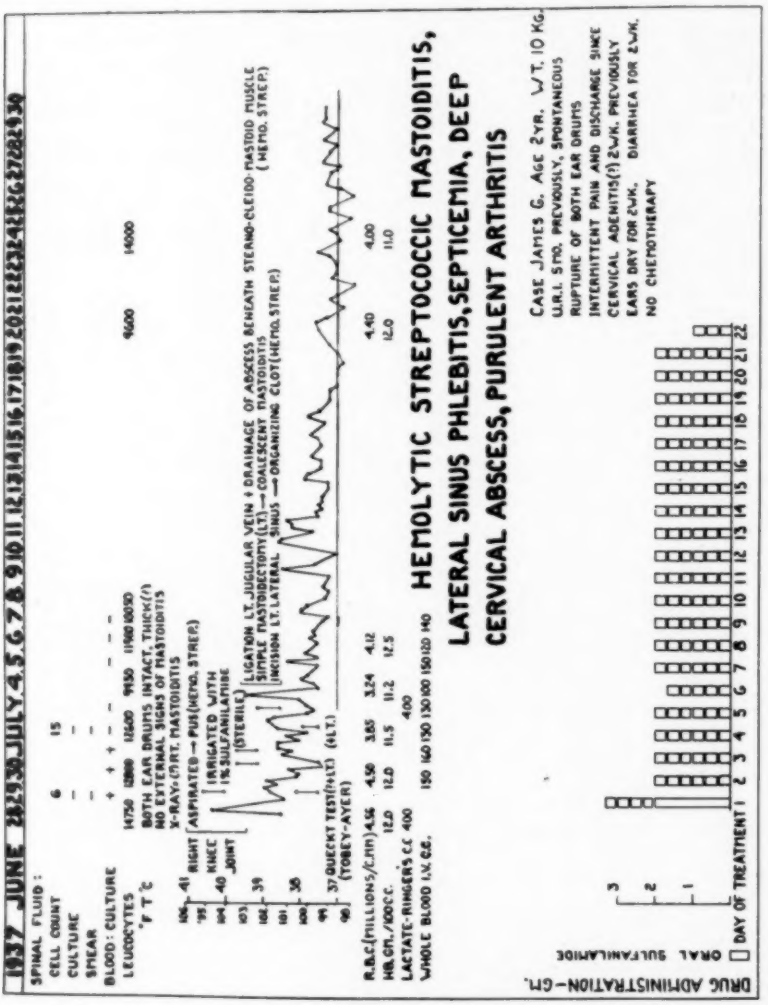

1937 JUNE 28 29 30 JULY 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
SPINAL FLUID:
CELL COUNT 6 15
CULTURE — —
SMEAR — —
BLOOD: CULTURE + + + — — — —
LEUCOCYTES 14750 12800 12600 9450 11900 10050 9600 14000
°F °C
BOTH EAR DRUMS INTACT. THICK(?)
NO EXTERNAL SIGNS OF MASTOIDITIS
X-RAY: (?) RT. MASTOIDITIS
106 41
105 RIGHT ASPIRATED → PUS (HEMO. STREP.)
104 40 KNEE JOINT IRRIGATED WITH 1% SULFANILAMIDE (STERILE)
103
102 39 LIGATION LT. JUGULAR VEIN + DRAINAGE OF ABSCESS BENEATH STERNO-CLEIDO MASTOID MUSCLE (HEMO. STREP.)
SIMPLE MASTOIDECTOMY (LT.) — COALESCENT MASTOIDITIS
101 INCISION LT. LATERAL SINUS — ORGANIZING CLOT (HEMO. STREP.)
100 38
99
98 37 QUICKY TEST (%LT) (4 LT.)
(TOBEY-AYER)
R.B.C. (MILLIONS/C.MM.) 4.56 4.50 3.85 3.24 4.12 4.40 4.00
HB GM./100 C.C. 12.0 12.0 11.5 11.2 12.5 12.0 11.0
LACTATE-RINGER'S C.C. 400 400
WHOLE BLOOD I.V. C.C. 150 160 130 100 150 120 140
HEMOLYTIC STREPTOCOCCIC MASTOIDITIS, LATERAL SINUS PHLEBITIS, SEPTICEMIA, DEEP CERVICAL ABSCESS, PURULENT ARTHRITIS
CASE JAMES G. AGE 2 YR. WT. 10 KG.
U.R.I. STR. PREVIOUSLY, SPONTANEOUS RUPTURE OF BOTH EAR DRUMS
INTERMITTENT PAIN AND DISCHARGE SINCE CERVICAL ADENITIS (?) 2 WK. PREVIOUSLY
EARS DRY FOR 2 WK. DIARRHEA FOR 2 WK.
NO CHEMOTHERAPY
DRUG ADMINISTRATION—GM.
ORAL SULFANILAMIDE
3
2
1
DAY OF TREATMENT 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Chart 2.

Supportive therapy in this case consisted of whole blood transfusions daily during the first few days of the illness and additional fluid and electrolyte in the form of lactate-Ringer's solution.

CASE 3 (Chart 3 and Table I).—M. McG., who was 11 years old when admitted, had a history of repeated attacks of otitis media from infancy, with intermittent pain and drainage from either or both ears. On Jan. 7, 1938, three weeks before

entry, he developed an acute generalized upper respiratory infection, and on Jan. 11 the left eardrum ruptured spontaneously. During this time he continued to have a low-grade, nonseptic fever and gradually became weaker and more listless. No chemotherapy was given prior to admission. He was admitted to the hospital from the outpatient clinic on Jan. 28.

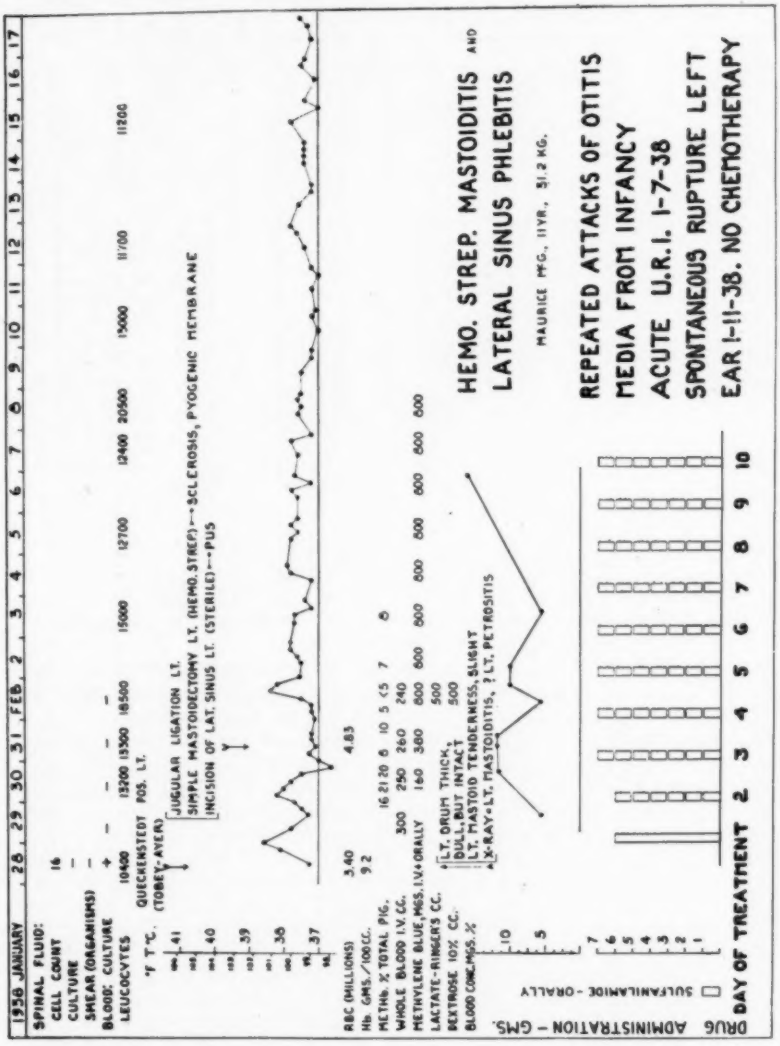

1938 JANUARY 28 29 30 31 FEB. 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
SPINAL FLUID:
CELL COUNT 16
CULTURE –
SMEAR (ORGANISMS) –
BLOOD: CULTURE + – – – –
LEUCOCYTES 10400 13200 13500 18500 15000 12700 12400 20500 15000 11700 11200
QUECKENSTEDT POS. LT.
(TOBEY-AYER)
°F T °C.
JUGULAR LIGATION LT.
SIMPLE MASTOIDECTOMY LT. (HEMO. STREP.)--SCLEROSIS, PYOGENIC MEMBRANE
INCISION OF LAT. SINUS LT. (STERILE)--PUS
RBC (MILLIONS) 3.40 4.83
Hb. GMS./100 CC. 9.2
METHB. % TOTAL PIG. 16 21 20 8 10 5 <5 7 6
WHOLE BLOOD I.V. CC. 300 250 260 240
METHYLENE BLUE MGS. I.V. ORALLY 160 360 600 600 600 600 600 600 600 600
LACTATE-RINGER'S CC. 500
DEXTROSE 10% CC. 500
BLOOD CONC. MGS. %
LT. DRUM THICK, DULL, BUT INTACT
LT. MASTOID TENDERNESS, SLIGHT
X-RAY: LT. MASTOIDITIS, ? LT. PETROSITIS
HEMO. STREP. MASTOIDITIS AND LATERAL SINUS PHLEBITIS
MAURICE MG., 11 YR., 51.2 KG.
REPEATED ATTACKS OF OTITIS MEDIA FROM INFANCY
ACUTE U.R.I. 1-7-38
SPONTANEOUS RUPTURE LEFT EAR 1-11-38. NO CHEMOTHERAPY
DRUG ADMINISTRATION – GMS.
SULFANILAMIDE - ORALLY
DAY OF TREATMENT 2 3 4 5 6 7 8 9 10

Chart 3.

Initial examination revealed the following: No elevation of temperature when first taken; intact but dull, thick, and bulging left eardrum; slight tenderness over the left mastoid; a frankly positive Tobey-Ayer test on the left; positive blood culture for hemolytic streptococci; leucocyte count of 10,400 with slight left shift;

TABLE

SULFONAMIDE-TREATED PATIENTS WITH LATERAL

CASE NO.	DATE OF ADM.	NAME	HISTORY NO.	SEX	AGE (YR.)	WT. (KG.)	PURULENT OTITIS MEDIA		MASTOIDITIS			
									EXT. SIGNS		X-RAY SIGNS	
							L.	R.	L.	R.	L.	R.
Recovered												
1	6/11/37	A. H.	N-964	F.	4	14	–	+	–	?		+
2	6/28/37	J. G.	N-1103	M.	2	10	–	–	–	–	–	?
3	1/28/38	M. McG.	O-262	M.	11	31	–	–	–	?	+	–
4	2/17/38	J. M.	O-398	M.	6	20	+	–	?	–	+	–
5	2/17/38	C. S.	O-401	M.	4	13	+	–	–	–	+	+
6	2/19/38	M. W.	O-414	F.	8	22	–	–	–	–	+	+
7	4/29/38	L. S.	O-849	F.	7	16	+	+	–	–	–	+
8	1/ 3/39	D. M.	P-114	M.	7	22	–	?	–	–	–	+
9	3/14/39	A. M.	P-567	F.	10	27	–	–	–	–	–	+
10	5/29/39	R. C.	P-1145	M.	11	28	–	–	?	–	+	–
11	2/15/40	J. M.	Q-328	M.	8	15	–	+	–	–	+	–
12	5/ 9/40	R. D.	P-2028	M.	12	42	–	–	–	–	+	+
13	6/19/39	J. R.	P-1314	F.	9	?	–	–	–	?		?
14	5/11/38	W. B.	P-937	M.	4	17	+	–	–	–	+	?
15	1/29/40	M. M.	Q-237	F.	2	12	–	+	–	+	?	+
16	5/ 9/40	D. H.	Q-381	F.	6	15	+	–	–	–	+	+
17	10/ 3/40	R. M. P.	Q-2128	F.	6	12	+	+	?	?	–	+
Fatal												
18	11/26/37	G. E.	N-2146	F.	2	10	+	–	+	–	+	–
19	12/20/37	J. I.	N-2242	M.	7	20	+	–	?	–	+	–

*Irregularly sustained fever.
S = Sulfanilamide.
P = Prontosil.
SP = Sulfapyridine.
ST = Sulfathiazole.
SMT = Sulfamethylthiazole.

and x-ray evidence of mastoiditis on the left side with questionable signs of left petrositis also. The spinal fluid was sterile with 16 cells per cubic millimeter. Treatment was instituted with oral sulfanilamide in amounts averaging 0.2 Gm. per kilogram per day, on which dose blood concentrations ranging from 5 to 15 mg. per 100 c.c. were obtained. The temperature was never septic in nature, but with the history and findings in keeping with mastoiditis and lateral sinus phlebitis and because of positive blood culture in the absence of otherwise adequate cause, left mastoidectomy with ligation of the left jugular vein was performed on Jan. 31, the fourth day of treatment, by Dr. Robert Votaw. Sclerosing of the mastoid cortex with pyogenic membrane lining the cells was found, and in addition there was pus within the lumen of a thrombosed lateral sinus. Hemolytic streptococci were cultured from the mastoid, but the pus from the sinus proved sterile. There were no further positive blood cultures after the one on the first day. As in the two preceding cases, frequent whole blood transfusions were given to maintain red cells and hemoglobin. Methylene blue was administered to control the rather considerable cyanosis from methemoglobinemia, which sometimes amounted to as much as 20 per cent of the total pigment. Recovery was uneventful and chemotherapy was discontinued on the tenth day.

CASE 4 (Chart 4 and Table I).—J. M., aged 5 years, became acutely ill with scarlet fever on Feb. 4, 1938. Rash and high fever persisted for three days. The latter then subsided somewhat, but not to normal, and on Feb. 12, a left myringot-

I

SINUS PHLEBITIS AND THROMBOSIS

TOBEY-AYER TESTS				BACTERIAL CULTURES							SULFONAMIDE	DURATION OF FEVER OVER 38° C. (DAYS)	BACTERIAL ETIOLOGY
FIRST		LATER		EAR		MAST.		SINUS		BLOOD			
L.	R.	L.	R.	L.	R.	L.	R.	L.	R.				
Cases													
−	?	−	+						+	+ (5)	S	15*	
?	−	+	−					+		+ (3)	S	13*	
+	−					+		−		+ (1)	S	5	
+	−			+						− (1)	S	17	
+	−	+	−			+		+		− (4)	S	9	
−	−	−	−							+ (1)	S	2	
+	?	−	+	−	+		+			+ (3)	S	11	Strep. hemolyticus
+	−	+	−		+		+		+	+ (1)	SP + S	25*	
+	−	+					−		+	+ (2)	SP	9	
+	+	−								+ (2)	SP + S	14	
−	−	+			+		−			+ (1)	SMT + S	21	
−	+	−		+		−				+ (1)	S	30*	
+	−	+							−	− (2)	S	8	Undetermined
−	?	−	−							+ (1)	S + P	29*	Strep. viridans
?	−	−	−	−			+			− (2)	SMT	44*	Pn. III
+	−					+		+		− (3)	SMT + SP	9	B. proteus and B. aerogenes
+	−				+	+	−			− (4)	ST + SP	16	B. proteus
Cases													
−	−	−	−	+		+				+ (1)	S	20	Staph. aureus + anaerobic streptococcus + gram-neg. bacillus
+	−			+				+		+ (30)	S + P	37	Hemo. strep.

omy was performed. No drainage was obtained; myringotomy was repeated on Feb. 16, with a flow of pus this time. Purulent drainage continued up to the time of entry on Feb. 17. On the day just previous to admission 1.33 Gm. of sulfanilamide was given orally.

The initial examination revealed a moderately ill child with tonsillitis, cervical adenitis, and tenderness over the left mastoid. The left ear was draining pus through an adequate incision. X-ray showed cloudiness but with apparently intact trabeculae of the left mastoid. Leucocytosis of 35,000 with a slight left shift was present. All blood cultures were negative, but cultures of ear and throat showed hemolytic streptococci. In spite of chemotherapy with oral sulfanilamide in doses of 0.2 Gm. per kilogram per day, marked elevation of temperature persisted. This was thought to be due to the cervical adenitis for a period of nine days. Then since the temperature became more septic in type and signs of mastoid involvement persisted, left mastoidectomy was decided upon. At the time of operation on March 3, with the patient under anesthesia, a lumbar puncture was made and the Tobey-Ayer test was found to be frankly positive. Left simple mastoidectomy with ligation of the jugular vein in the neck was then performed by Dr. A. B. Potter. Antral and tip cell necrosis and considerable granulation tissue were found, but the small portion of exposed lateral sinus appeared normal and was not incised. No cultures were made. The temperature following operation fell promptly and was normal in forty-eight hours and remained so when chemotherapy was discontinued. X-rays repeated on Feb. 15, 1938, were interpreted as showing petrositis on the left.

CASE 5 (Chart 5 and Table I).—This 4-year-old boy, C. S., had a history of earaches following measles two months previously. He became ill with a rash, fever, and sore throat diagnosed as scarlet fever eleven days before entry to the hospital. Three days later, eight days prior to admission, bilateral cervical swellings ap-

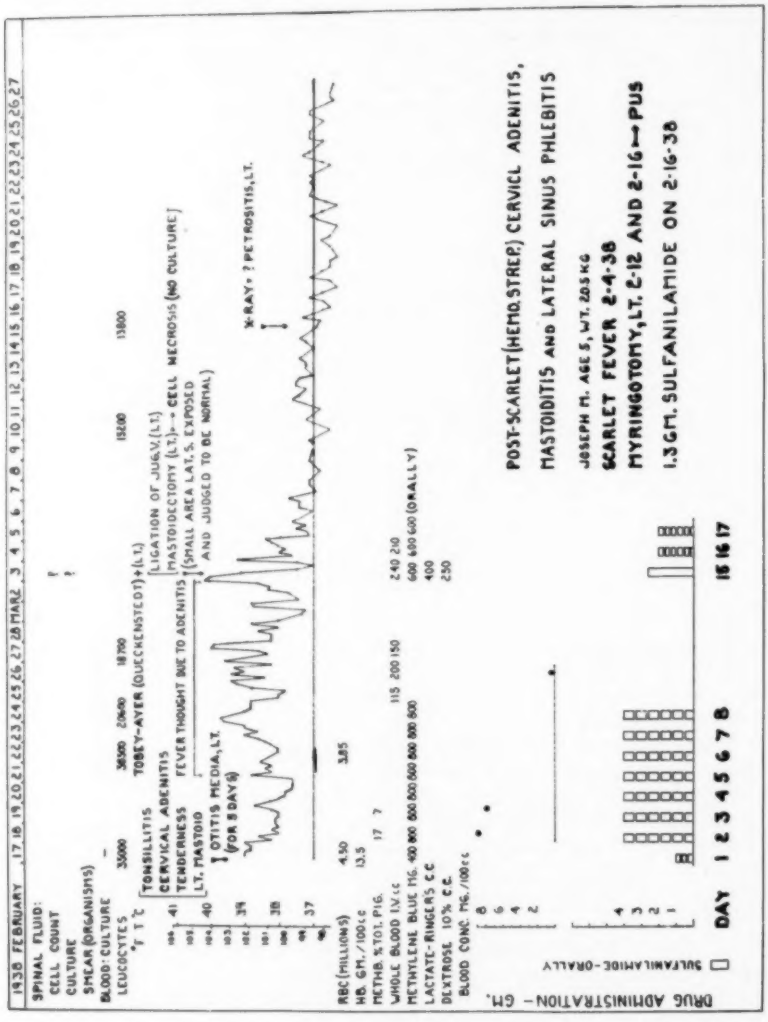

1938 FEBRUARY 17 18 19 20 21 22 23 24 25 26 27 28 MARCH 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
SPINAL FLUID:
CELL COUNT
CULTURE
SMEAR (ORGANISMS)
BLOOD CULTURE
LEUCOCYTES
35000 38500 20600 18700 15200 13800
TOBEY-AYER (DUECKENSTEDT)+(LT.)
TONSILLITIS
CERVICAL ADENITIS
TENDERNESS
LT. MASTOID
LIGATION OF JUG.V.(LT.)
MASTOIDECTOMY (LT.)→ CELL NECROSIS (NO CULTURE)
FEVER THOUGHT DUE TO ADENITIS
SMALL AREA LAT. S. EXPOSED
AND JUDGED TO BE NORMAL)
OTITIS MEDIA, LT.
(FOR 5 DAYS)
X-RAY: ? PETROSITIS, LT.
RBC (MILLIONS) 4.50 3.85
HB. GM. /100 c.c. 13.5
METHB. % TOL. PIG. 17 7
WHOLE BLOOD I.V. c.c. 115 200 150 240 210
METHYLENE BLUE I.V. 400 800 800 800 800 800 800 800 600 600 600 (SMALLER)
LACTATE-RINGER'S C.C. 400
DEXTROSE 10% C.C. 250
BLOOD CONC. MG. /100 c.c.
8
6
4
2
POST-SCARLET (HEMO. STREP.) CERVICL ADENITIS,
MASTOIDITIS AND LATERAL SINUS PHLEBITIS
JOSEPH M. AGE 5, WT. 20.5 KG
SCARLET FEVER 2-4-38
MYRINGOTOMY, LT. 2-12 AND 2-16→ PUS
1.3 GM. SULFANILAMIDE ON 2-16-38
4
3
2
1
DRUG ADMINISTRATION – GM.
SULFANILAMIDE - ORALLY
DAY 1 2 3 4 5 6 7 8 15 16 17

Chart 4.

peared. Pain recurred in the left ear, and the next day there was spontaneous rupture of the left eardrum with subsequent purulent drainage. The child had neither eaten nor taken fluids well during the illness and was having difficulty with breathing and swallowing. Some sulfonamide chemotherapy may have been given.

On admission on Feb. 17, 1938, examination revealed an acutely ill boy who was listless and showed marked loss of hearing. There was typical postscarlet desquamation of the skin, moderate dehydration, bilateral cervical adenitis, and pus draining from a large perforation of the left drum. The temperature on admission was very high, and the child appeared very toxic. The leucocyte count

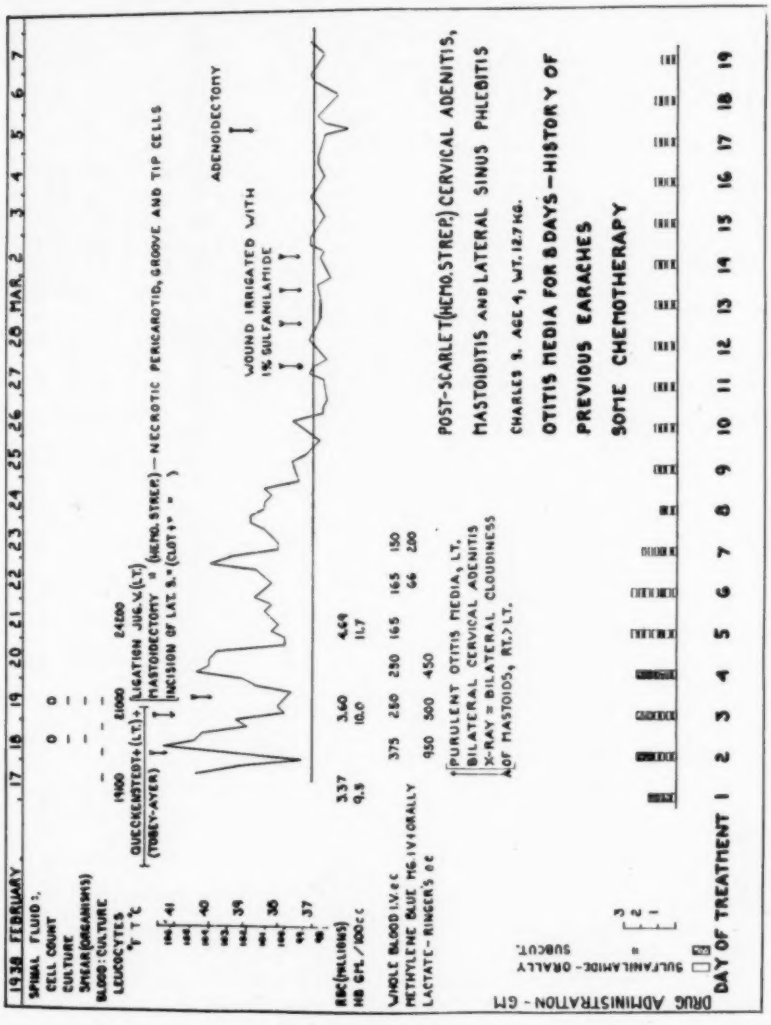

1938 FEBRUARY
17 18 19 20 21 22 23 24 25 26 27 28 MAR. 2 3 4 5 6 7
SPINAL FLUID:
CELL COUNT
CULTURE
SMEAR (ORGANISMS)
BLOOD: CULTURE
LEUCOCYTES
1900 21000 24200
QUECKENSTEDT+ (L.T.)
(TOBEY-AYER)
LIGATION JUG.V.(L.T.)
MASTOIDECTOMY + (MENG. STREP.) — NECROTIC PERICAROTID, GROOVE AND TIP CELLS
INCISION OF LAT. S.+ (CLOT+ " ")
ADENOIDECTOMY
WOUND IRRIGATED WITH 1% SULFANILAMIDE
RBC (MILLIONS)
HB GM. / 100 cc
WHOLE BLOOD IV cc
METHYLENE BLUE IM IV ORALLY
LACTATE-RINGER'S cc
PURULENT OTITIS MEDIA, LT.
BILATERAL CERVICAL ADENITIS
X-RAY = BILATERAL CLOUDINESS OF MASTOIDS, RT.>LT.
POST-SCARLET (HEMO. STREP.) CERVICAL ADENITIS, MASTOIDITIS AND LATERAL SINUS PHLEBITIS
CHARLES S. AGE 4, WT. 12.7 KG.
OTITIS MEDIA FOR 8 DAYS — HISTORY OF PREVIOUS EARACHES SOME CHEMOTHERAPY
DRUG ADMINISTRATION - GM
SULFANILAMIDE - ORALLY
SUBCUT.
DAY OF TREATMENT

Chart 5.

was 19,100 with moderate left shift. X-ray showed evidence of bilateral mastoiditis with density about the canals on either side and poorly defined cellular structure, more marked on the right. There was also questionable papilledema on the right. Blood cultures were all negative. The Tobey-Ayer test was per-

formed twice, on Feb. 18 and 19, and was frankly positive on each occasion. The temperature for the next two days was high and septic in type. On Feb. 19, the third day of treatment, ligation of the left jugular vein in the neck and left mastoidectomy with incision of the lateral sinus were performed by Dr. A. J. Cone. At operation necrotic pericarotid, groove and tip cells, and an organizing

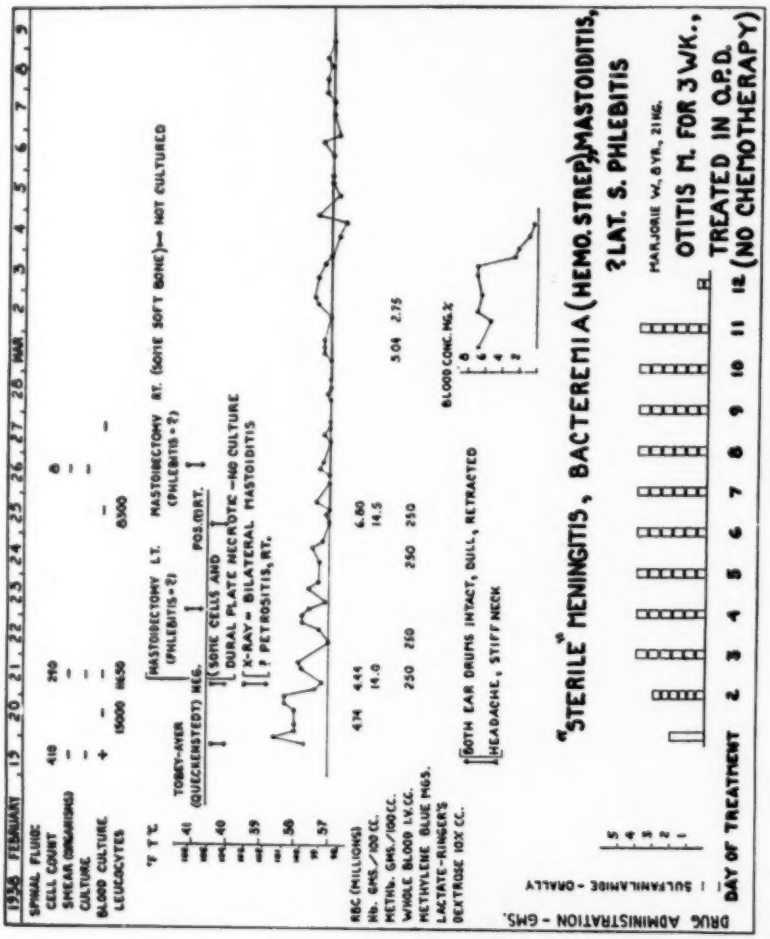

1936 FEBRUARY 19 20 21 22 23 24 25 26 27 28 MAR. 2 3 4 5 6 7 8 9
SPINAL FLUID:
CELL COUNT 410 250 0
SMEAR (ORGANISMS) - - -
CULTURE - - -
BLOOD CULTURE + - - - -
LEUCOCYTES 15000 11450 8300
°F °C
TOBEY-AYER (QUECKENSTEDT) NEG.
MASTOIDECTOMY LT. (PHLEBITIS-?)
POS. M.R.T.
MASTOIDECTOMY RT. (SOME SOFT BONE)— NOT CULTURED (PHLEBITIS-?)
SOME CELLS AND DURAL PLATE NECROSIS —NO CULTURE
X-RAY — BILATERAL MASTOIDITIS ? PETROSITIS, RT.
RBC (MILLIONS) 4.74 4.44 6.80
Hb. GMS./100 CC. 14.0 14.5
METHb. GMS./100 CC. 5.04 2.75
WHOLE BLOOD I.V. CC. 250 250 250 250
METHYLENE BLUE MGS.
LACTATE-RINGER'S
DEXTROSE 10% CC.
BOTH EAR DRUMS INTACT, DULL, RETRACTED
HEADACHE, STIFF NECK
BLOOD CONC. MG.%
"STERILE" MENINGITIS, BACTEREMIA (HEMO. STREP.) MASTOIDITIS, ?LAT. S. PHLEBITIS
MARJORIE W., 6 YR., 21 KG.
OTITIS M. FOR 3 WK., TREATED IN O.P.D. (NO CHEMOTHERAPY)
DRUG ADMINISTRATION - GMS.
SULFANILAMIDE - ORALLY
DAY OF TREATMENT 2 3 4 5 6 7 8 9 10 11 12

Chart 6.

clot in the lateral sinus were found. Both mastoid and lateral sinus cultures were positive for hemolytic streptococci. Chemotherapy was begun on the day of admission with oral and subcutaneous sulfanilamide in amounts averaging 0.2 Gm. per kilogram per day. The postoperative course was uneventful with rapid subsidence of the fever. The wound was irrigated three times with a 1 per cent solution of sulfanilamide in Ringer's solution with very rapid healing. Considerable supportive treatment was necessary especially for the first few days. This

was in the form of frequent whole blood transfusions and lactate-Ringer's solution. Cyanosis was controlled by the administration of methylene blue administered both orally and intravenously.

CASE 6 (Chart 6, Table I).—M. W., 8 years old, had developed earache three weeks previous to admission. Five days later the left drum ruptured spontaneously, and two days after that the right drum was incised. She was treated for ten days in the outpatient clinic without chemotherapy. Drainage from both ears ceased seven days prior to hospital entry, but the left ear drained again for a short while three or four days later. She also had complained of severe headache and dizziness and had appeared drowsy to her parents.

On the initial examination on Feb. 19, 1938, both eardrums were found dull, thickened, and retracted, but intact. She was complaining of headache and there was a stiff neck. The leucocyte count was 15,000 with slight left shift, and the spinal fluid contained 410 cells per cubic millimeter, but no organisms were seen. The initial blood culture was positive for hemolytic streptococci, but the spinal fluid culture was sterile. The Tobey-Ayer test was negative. X-rays showed bilateral cloudiness of the mastoids with possible erosion of cellular structure on the left and some haziness of the petrous apex on the right side. Simple left mastoidectomy was done on Feb. 23 by Dr. Robert Votaw, revealing some mastoid cells containing pyogenic membrane, necrotic cells and dural plate, and some grayness of the wall of the lateral sinus. The latter did not appear thrombosed and was not incised. No cultures were made. Postoperatively there was no elevation of temperature and blood cultures remained negative. On Feb. 26 a right simple mastoidectomy was done, revealing soft bone and a few cells containing pyogenic membrane and a similar discoloration of the sinus wall. The child was treated during this period with oral sulfanilamide and frequent whole blood transfusions.

CASE 7 (Chart 7 and Table I).—This 7-year-old girl, L. S., had a generalized upper respiratory infection two weeks before admission. Two days later she complained of earache. Bilateral myringotomy was done, and pus was obtained from the right ear. At this time only bloody fluid was obtained from the left ear, but five days later it also began to discharge pus. Two days later she began to complain of pain and tenderness behind the right ear which lasted two or three days. On the same day a rash appeared over the body which was suggestive of scarlet fever. Sulfanilamide was given in the amount of 2.6 Gm. on April 25, 1938, and for the next two days there was no elevation of temperature. On the night before entry to the hospital, the temperature suddenly rose to 105° F., and she was admitted the next day, April 29.

The initial examination showed an acutely ill, prostrated child with high fever. There was an erythematous rash over the body which was fading, and her throat and tongue were compatible with a diagnosis of scarlet fever. Bilateral purulent otitis media without external signs of mastoiditis was present. The leucocyte count was 12,000 with a definite left shift. X-ray findings of hazy cellular structure and poorly defined trabeculae on the right pointed to a mastoiditis on that side. The initial and two subsequent blood cultures were positive for hemolytic streptococci. A Tobey-Ayer test attempted on the following morning was suggestively positive on the left but not conclusive because of failure of the patient to cooperate. This was repeated the next day under ether anesthesia and revealed a complete block on the left side.

Chemotherapy was begun shortly after admission with orally administered sulfanilamide without favorable response as the temperature remained markedly

elevated and the blood cultures positive. On May 1 the third day of treatment a ligation of the left jugular vein in the neck with left simple mastoidectomy and incision of the lateral sinus was performed by Dr. A. B. Potter. Pyogenic membrane, soft trabeculae, and a gray lateral sinus were found. No cultures were made. Postoperatively the temperature remained markedly elevated with little improvement in the patient's condition. On May 7 the temperature rose to over

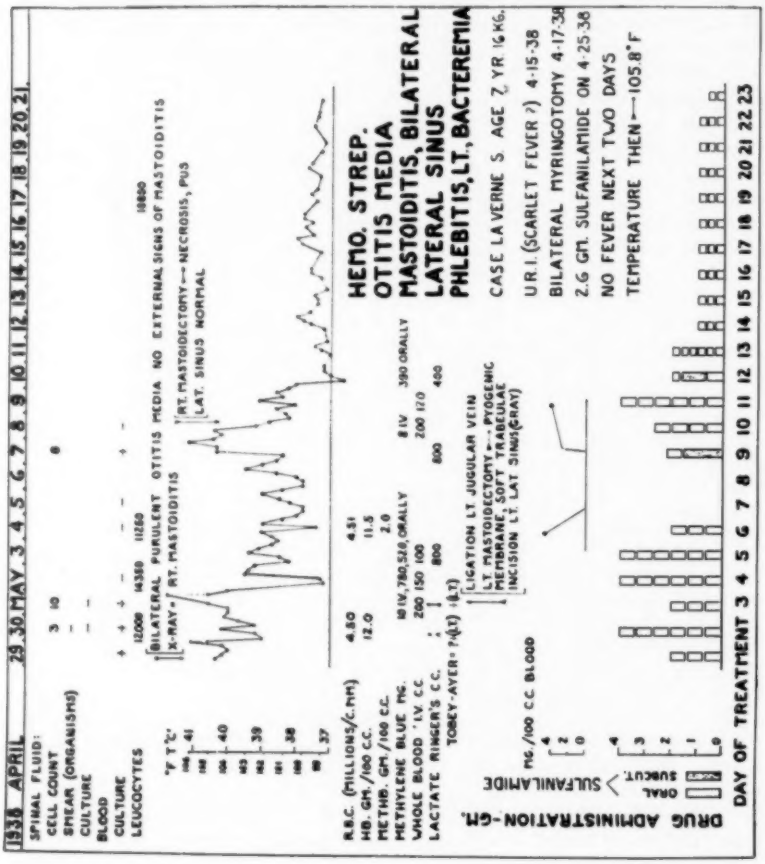

1936 APRIL 29,30 MAY 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
SPINAL FLUID:
CELL COUNT
SMEAR (ORGANISMS)
CULTURE
BLOOD
CULTURE
LEUCOCYTES
12000 14300 11250 10800
BILATERAL PURULENT OTITIS MEDIA NO EXTERNAL SIGNS OF MASTOIDITIS
X-RAY RT. MASTOIDITIS
RT. MASTOIDECTOMY — NECROSIS, PUS
LAT. SINUS NORMAL
HEMO. STREP. OTITIS MEDIA
MASTOIDITIS, BILATERAL
LATERAL SINUS PHLEBITIS, LT., BACTEREMIA
R.B.C. (MILLIONS/C.MM) 4.80 4.51
HB. GM./100 C.C. 12.0 11.5
METHB. GM./100 C.C. 2.0
METHYLENE BLUE MG. 10 IV., 780, 520, ORALLY 8 IV. 390 ORALLY
WHOLE BLOOD I.V. C.C. 200 150 100 200 170
LACTATE RINGER'S C.C. 800 800 400
TOBEY-AYER PAT.
LIGATION LT. JUGULAR VEIN
LT. MASTOIDECTOMY — PYOGENIC MEMBRANE, SOFT TRABECULAE INCISION LT. LAT. SINUS (GRAY)
CASE LA VERNE S. AGE 2 YR. 16 MO.
U.R.I. (SCARLET FEVER ?) 4-15-38
BILATERAL MYRINGOTOMY 4-17-38
2.6 GM. SULFANILAMIDE ON 4 25 38
NO FEVER NEXT TWO DAYS
TEMPERATURE THEN — 105.8° F
DRUG ADMINISTRATION-GM.
SULFANILAMIDE
ORAL
SUBCUT.
MG./100 C.C. BLOOD
DAY OF TREATMENT 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23

Chart 7.

41° C., and another positive blood culture was obtained. On the following day a right simple mastoidectomy was performed, revealing necrosis and pus of the mastoid cells but a normal lateral sinus. The temperature then fell promptly to normal in forty-eight hours and remained so throughout the remainder of her hospital stay.

Frequent whole blood transfusions, parenteral fluid, and electrolyte were given as supportive therapy. Some of the sulfanilamide during the postoperative course was incorporated with subcutaneously administered lactate-Ringer's solution. Considerable methylene blue was given orally and intravenously to control the methemoglobinemia.

It should be noted in this case that there were local collections of pus in both mastoids which necessitated surgical drainage before sulfanilamide was completely effective in controlling the infection. This is consistent with all that we now know about the ineffectiveness of chemotherapy in sterilizing collections of frank pus.

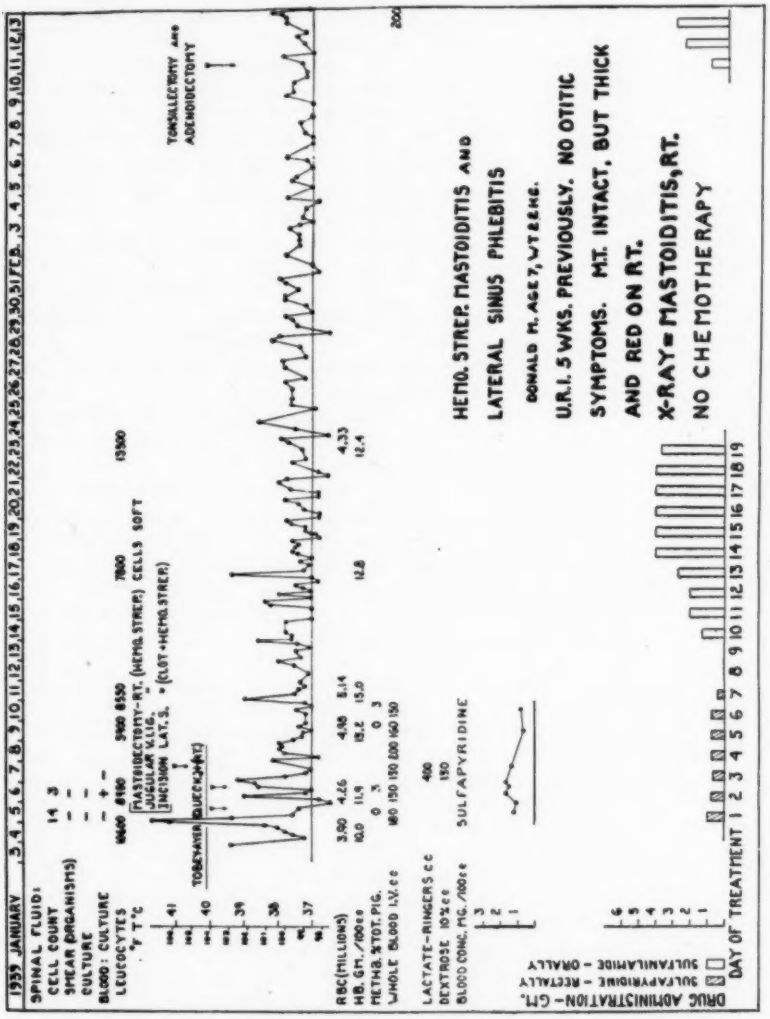

1939 JANUARY 3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31/FEB. 1,2,3,4,5,6,7,8,9,10,11,12,13
SPINAL FLUID:
CELL COUNT 14 3
SMEAR (ORGANISMS) - -
CULTURE - -
BLOOD: CULTURE - + -
LEUCOCYTES 9600 8100 5900 8550 7000 13500
°F °C
MASTOIDECTOMY-RT. (HEMO. STREP.) CELLS SOFT
JUGULAR V. LIG.
INCISION LAT. S. + (CLOT + HEMO. STREP.)
TONSILLECTOMY AND ADENOIDECTOMY
TOBEY-MYER BLOCK (RT.)
RBC (MILLIONS) 3.90 4.26 4.98 5.14 4.33
HB. GM./100cc 10.0 11.9 13.2 15.0 12.4
METHB. %TOT. PIG. 0 3 0 3
WHOLE BLOOD LV. cc 180 150 180 200 160 150
LACTATE-RINGERS cc 400
DEXTROSE 10% cc 150
BLOOD CONC. MG./100cc SULFAPYRIDINE
HEMO. STREP. MASTOIDITIS AND LATERAL SINUS PHLEBITIS
DONALD M. AGE 7, WT. 52 LBS.
U.R.I. 5 WKS. PREVIOUSLY. NO OTITIC SYMPTOMS. MT. INTACT, BUT THICK AND RED ON RT.
X-RAY = MASTOIDITIS, RT.
NO CHEMOTHERAPY
DRUG ADMINISTRATION - GM.
SULFAPYRIDINE - RECTALLY
SULFANILAMIDE - ORALLY
DAY OF TREATMENT 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

Chart 8.

CASE 8 (Chart 8 and Table I).—This 7-year-old boy, D. M., had a generalized upper respiratory infection five weeks before hospital admission. This had apparently cleared, but he appeared listless and later was observed to hold his head to the right side and complain of a little stiffness of his neck. Ten days before entry he began to have an irregular, high and septic type of temperature with

rise on one occasion to 106.5° F. He complained of pain in the ear only once, at the onset of fever, but not again. Later questioning elicited a history of a discharging ear four years previously and two subsequent attacks of earache, in September and December, 1938, each lasting several days.

The initial examination on Jan. 3, 1939, revealed intact eardrums, but with the right one red, thick, and bulging. The temperature was quite high, being 39° C. No resistance to motion of the neck was found, but there was some pain on extreme flexion. X-ray evidence pointed to mastoiditis on the right side with acumination of the cells at the tip and relatively poor cellular development. On Jan. 5, during the night his temperature rose rapidly to 107.5° F. but fell below normal by morning. Lumbar puncture done at this time revealed a positive Tobey-Ayer test on the right. The blood culture and the culture of the pus aspirated from the ear on Jan. 6 were positive for hemolytic streptococci. The spinal fluid contained 14 lymphocytes and was sterile.

Treatment was begun with sodium sulfapyridine per rectum in amounts totaling 0.2 Gm. per kilogram per day. On Jan. 7, the fourth day of treatment, the right jugular vein was ligated in the neck and right mastoidectomy was performed with incision of the lateral sinus by Dr. H. M. Smit. The vein was found completely thrombosed and suppurating at one point, and there was necrosis of the mastoid cells. Hemolytic streptococci were cultured from the lateral sinus pus. The temperature subsided following operation but not to normal. The mastoid wound healed rapidly, and the persisting low-grade temperature was thought due to infected maxillary sinuses which were present. Treatment was changed from rectal sodium sulfapyridine to oral sulfanilamide on the tenth day of treatment. General supportive treatment was administered with whole blood transfusions, dextrose, and subcutaneous lactate-Ringer's solution. With chemotherapy entirely in the form of sulfapyridine, only a slight degree of methemoglobinemia, amounting to about 3 per cent of the total pigment, developed, and it was not necessary to employ methylene blue therapy. Before he left the hospital, his maxillary antra were irrigated, and tonsillectomy and adenoidectomy were performed. He was discharged in excellent condition.

CASE 9 (Chart 9 and Table I).—A. M., 10 years old on admission, had a history of otitis media for sixteen days, beginning with severe pain in the right ear on Feb. 27, 1939, with myringotomy two days later. Discharge was profuse from the draining ear, but it had decreased somewhat in amount just before entry. However, eleven days prior to hospital admission, she began to have repeated chills associated with high fever once or twice daily. The temperature was irregular and septic in type, ranging from 98 to 106° F. History also revealed that three years previously there was spontaneous perforation of the right ear followed by a discharge for two weeks. She had also complained of pain in the right ankle and thigh for about one week. Sulfanilamide in amounts of about 2 Gm. daily was started four days before admission.

The initial hospital examination revealed an acutely ill child with a temperature of 39° C. The right drum was intact but thickened and scarred, and there were no external signs of mastoiditis. X-ray examination showed cloudiness of the mastoid on the right side. A Tobey-Ayer test done on the second day was not conclusive but did not show as high a rise on the right as on the left. The leucocyte count was 10,600 with slight left shift, and the initial blood culture was positive for hemolytic streptococci. The spinal fluid findings were essentially normal. On March 16, the third day of treatment, the right jugular vein was ligated in the neck by Dr. H. M. Smit and followed by right mastoidectomy and incision of the lateral sinus. There was necrosis and pus in the mastoid cells,

and the lateral sinus was gray in appearance and contained an organizing thrombus. The pus from the mastoid was sterile on culture, but from the lateral sinus hemolytic streptococci were cultured. The temperature fell to normal in four days and remained so except for a few days of low-grade elevation just before discharge, not associated with any significant physical findings.

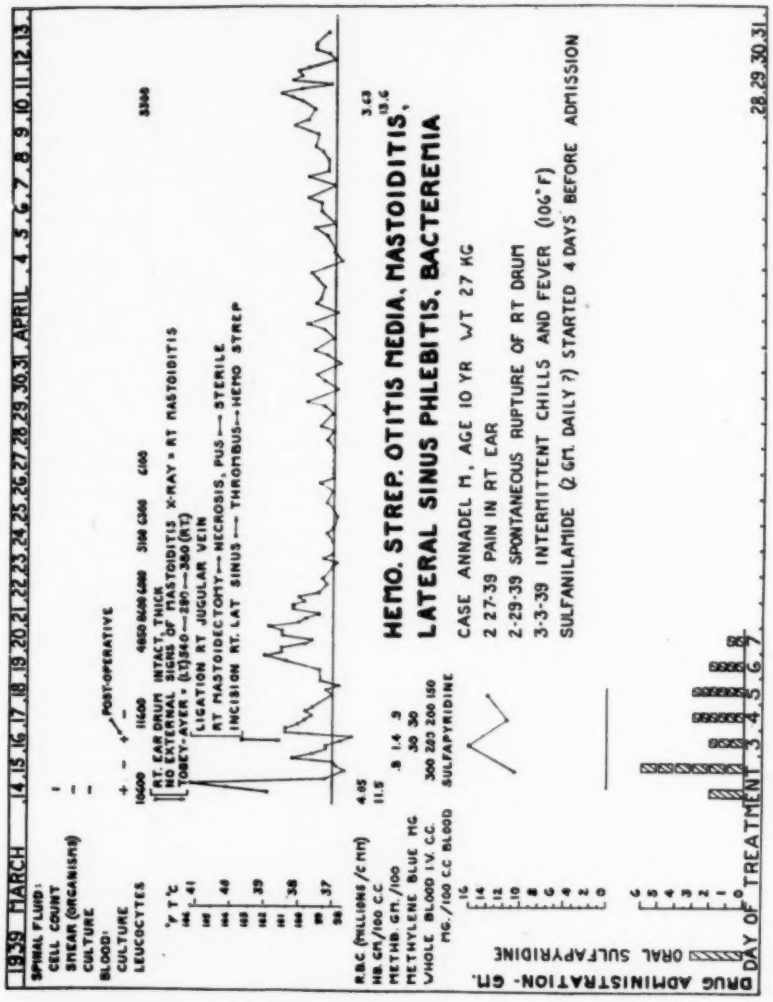

1939 MARCH 14.15.16.17.18.19.20.21.22.23.24.25.26.27.28.29.30.31 APRIL 1.2.3.4.5.6.7.8.9.10.11.12.13.
SPINAL FLUID:
CELL COUNT
SMEAR (ORGANISMS)
CULTURE
BLOOD:
CULTURE
LEUCOCYTES
POST-OPERATIVE
10600 11600 4650 8600 4800 3100 6300 6100 3300
RT. EAR DRUM INTACT, THICK
NO EXTERNAL SIGNS OF MASTOIDITIS X-RAY = RT MASTOIDITIS
TOBEY-AYER = (1:1)340—280—380 (RT)
LIGATION RT JUGULAR VEIN
RT MASTOIDECTOMY—NECROSIS, PUS—STERILE
INCISION RT. LAT SINUS—THROMBUS—HEMO STREP
HEMO. STREP. OTITIS MEDIA, MASTOIDITIS, 13.6
LATERAL SINUS PHLEBITIS, BACTEREMIA
CASE ANNADEL M., AGE 10 YR WT 27 KG
2-27-39 PAIN IN RT EAR
2-29-39 SPONTANEOUS RUPTURE OF RT DRUM
3-3-39 INTERMITTENT CHILLS AND FEVER (106° F)
SULFANILAMIDE (2 GM. DAILY ?) STARTED 4 DAYS BEFORE ADMISSION
R.B.C. (MILLIONS/C MM) 4.05 3.63
HB. GM/100 C.C. 11.5
METHB. GM./100 3 1.4 .3
METHYLENE BLUE MG. 30 30
WHOLE BLOOD I.V. C.C. 300 250 200 150
MG./100 C.C. BLOOD SULFAPYRIDINE
DRUG ADMINISTRATION - GM.
ORAL SULFAPYRIDINE
DAY OF TREATMENT 1.2.3.4.5.6.7.
28.29.30.31.

Chart 9.

Chemotherapy in this case consisted of oral doses of sulfapyridine on which blood concentrations from 10 to 16 mg. per 100 c.c. were obtained. Frequent small whole blood transfusions were also given and small amounts of methylene blue for mild cyanosis due to methemoglobinemia.

CASE 10 (Chart 10 and Table I).—This boy, R. C., 11 years old on admission, had a history of frequent colds accompanied by sore throats for many years. In

August, 1938, there occurred a spontaneous rupture of both drums, which drained for a few days and then healed. Subsequently, there was intermittent drainage from the ears with each fresh respiratory infection. On May 15, 1939, which was two weeks before hospital entry, he complained of pain in the left ear and

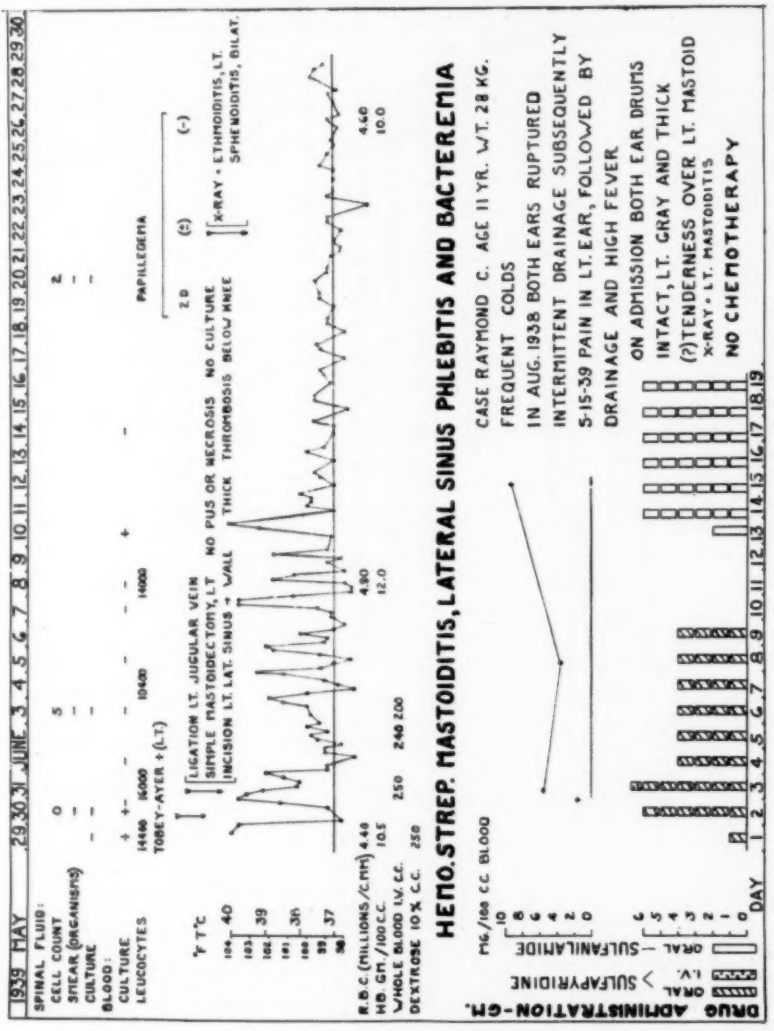

HEMO. STREP. MASTOIDITIS, LATERAL SINUS PHLEBITIS AND BACTEREMIA
CASE RAYMOND C. AGE 11 YR. WT. 28 KG.
FREQUENT COLDS
IN AUG. 1938 BOTH EARS RUPTURED
INTERMITTENT DRAINAGE SUBSEQUENTLY
5-15-39 PAIN IN LT. EAR, FOLLOWED BY
DRAINAGE AND HIGH FEVER
ON ADMISSION BOTH EAR DRUMS
INTACT, LT. GRAY AND THICK
(?)TENDERNESS OVER LT. MASTOID
X-RAY - LT. MASTOIDITIS
NO CHEMOTHERAPY
1939 MAY 29 30 31 JUNE 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
SPINAL FLUID:
CELL COUNT 0 5 2
SMEAR (ORGANISMS) - - - - -
CULTURE - - - - -
BLOOD:
CULTURE + +- - - - - + -
LEUCOCYTES 14400 15600 10400 10400 14000
TOBEY-AYER + (L.T.)
PAPILLEDEMA 2 D (±) (-)
LIGATION LT. JUGULAR VEIN
SIMPLE MASTOIDECTOMY, LT NO PUS OR NECROSIS NO CULTURE
INCISION LT. LAT. SINUS - WALL THICK THROMBOSIS BELOW KNEE
X-RAY - ETHMOIDITIS, LT. SPHENOIDITIS, BILAT.
°F °C
104 40
103 39
102 38
101 37
100 36
99 37
R.B.C. (MILLIONS/C.MM.) 4.40 4.90 4.60
HB. GM./100 C.C. 10.5 12.0 10.0
WHOLE BLOOD I.V. C.C. 250 240 200
DEXTROSE 10% C.C. 250
MG./100 C.C. BLOOD
SULFAPYRIDINE
SULFANILAMIDE
ORAL
I.V.
ORAL
DRUG ADMINISTRATION-GM.
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

Chart 10.

developed high fever. A few days later some discharge was noted from that side, and pain in the ear became quite severe. The temperature continued to be irregularly elevated and higher in the evening. No chemotherapy was given during the illness.

On admission on May 29 examination revealed an acutely ill child with a temperature of 40° C., intact eardrums but with the left drum gray and thick, and

questionable tenderness over the left mastoid. The leucocyte count was 14,400 without left shift. Blood culture taken on admission was positive for hemolytic streptococci. The x-rays showed marked increase in density about the canals on both sides and acumination of cells plus destruction of trabeculae on the left. A Tobey-Ayer test on the morning of May 30 was frankly positive on the left. The temperature continued septic in type, and on May 31 the left jugular vein was ligated in the neck, and simple left mastoidectomy with incision of the lateral sinus was performed by Dr. H. M. Smit. No pus or necrotic tissue was found, but there was granulation tissue in the mastoid antrum. The lateral sinus wall was thick and gray but compressible in the part uncovered in the temporal bone; the thrombosis was thought to be below the knee of the sinus. The vein was not incised. The temperature subsided somewhat during the next two days but later again became elevated with daily spikes. Chemotherapy was begun on the day of admission with oral sulfapyridine and continued through the ninth day. Soon after the drug was discontinued, the temperature rose higher and showed greater variation. On May 10, the thirteenth day of treatment, there was a sharp rise in temperature, and another blood culture positive for hemolytic streptococci was obtained. Accordingly, chemotherapy was resumed with oral doses of sulfanilamide and continued for the next seven days, the temperature falling promptly to normal and remaining so thereafter.

On June 19 an eye examination revealed two diopters papilledema of both optic discs. The eyegrounds had previously been negative except for some fullness of the veins. There were, however, no other abnormal neurologic findings, and the papilledema subsided within a few days and did not recur. The physical condition at the time of discharge on July 6, 1939, was excellent except for x-ray evidence of ethmoiditis on the left and bilateral sphenoiditis.

CASE 11 (Chart 11 and Table I).—This 7-year-old boy, J. M., developed a generalized acute upper respiratory infection on Feb. 11, 1940, which included bilateral otitis media. Just two days later meningeal symptoms began and admission to the hospital occurred on the third day of meningitis, Feb. 15, 1940. The initial examination revealed a very seriously and acutely ill boy with spinal fluid literally teeming with streptococci, proved later on culture to be hemolytic. Cell count of this initial tap was only 380. The Tobey-Ayer test was already positive on the right side, and the blood culture proved also to be positive on the day of admission. Treatment was started with a single dose of sodium sulfamethylthiazole followed by sulfamethylthiazole given orally. From the second through the fourteenth day of sulfonamide treatment both sulfamethylthiazole and sulfanilamide were administered, the total dosage averaging about 0.4 Gm. per kilogram of body weight per day. The temperature fell steadily after the beginning of treatment, and the boy showed gradual improvement. While organisms could not be seen in the spinal fluid on the second day and thereafter, they continued to grow on culture for the first six days, after which the spinal fluid continued to be sterile. As in previous cases of a similar nature, immediately after treatment the spinal fluid cell count rose as the number of organisms diminished, and then fell. On the seventh day of sulfonamide treatment, after the blood culture had been sterile for five days, and on the first day of sterile spinal fluid, ligation of the right internal jugular vein was made, and then a right simple mastoidectomy was performed with exposure and incision of the lateral sinus. Mastoid cells everywhere were found involved, granulations spread over the knee of the lateral sinus, and, where exposed, the dura was found red and thickened. The temperature then slowly returned toward normal. The spinal fluid continued to show some increase in cell count but remained without organisms to be seen and was always sterile, findings possibly to be explained by some remaining pocket of

infection. Strabismus and dilated pupils were the only neurologic findings suggestive of continued central nervous system involvement.

As in previous cases, there was need for considerable supportive treatment, especially early in the course of the infection, and for about thirteen days fluid was given by the continuous intravenous injection method consisting of dextrose

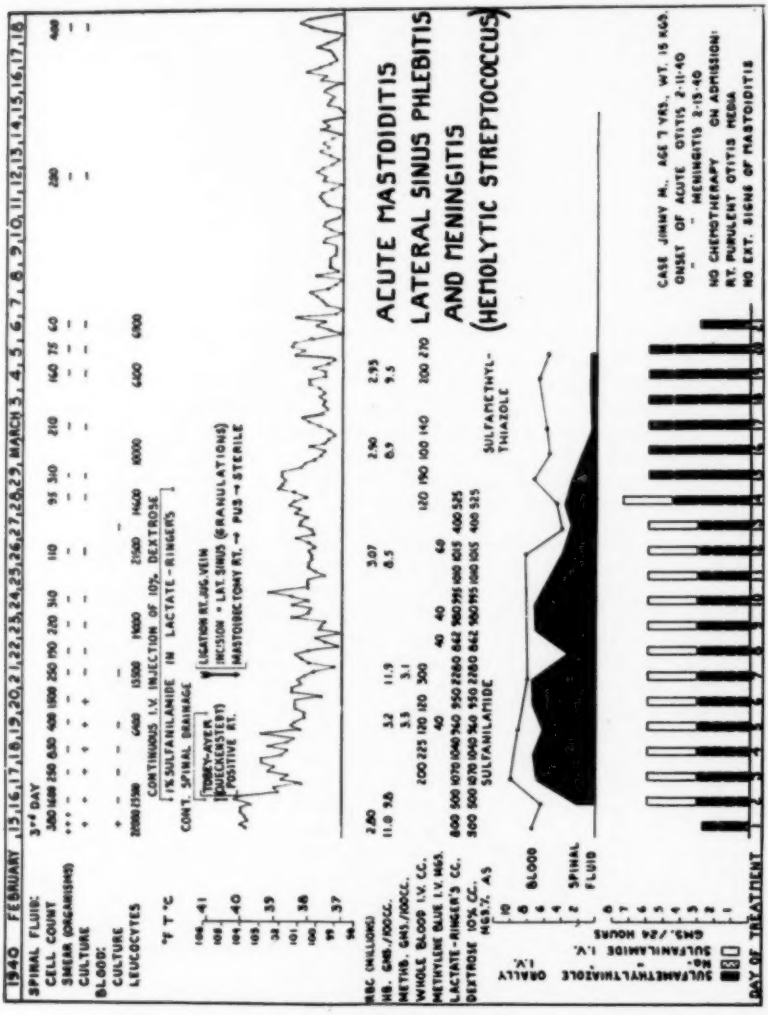


Chart 11.

and lactate-Ringer's solution to which sulfanilamide was added for the total sulfanilamide administration during this period. For the first four days continuous spinal fluid drainage was also effected. The spinal fluid concentrations averaged about 7 mg. per 100 c.c. during the period when organisms continued to be grown on culture. Also, as in some of the previous cases, a transient leuco-

penia was noted, the blood count dropping from 23,500 on Feb. 16 to 6,400 on Feb. 19. The dosage of the drug, however, was not reduced, and on Feb. 21 the count doubled. On April 6 the tonsils and adenoids were removed, and on April 17 the child was transferred to Ridge Farm, our country convalescent department, to complete his recovery. He was finally discharged from the hospital on June 19, 1940, completely recovered except for a dilated and fixed right pupil.

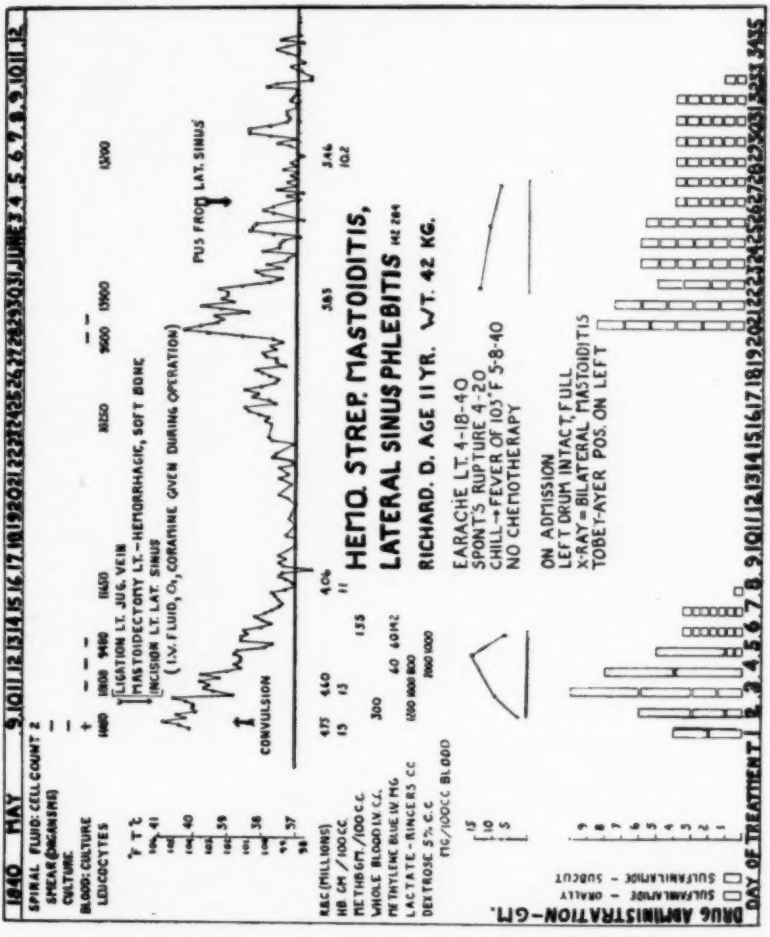


Chart 12.

CASE 12 (Chart 12 and Table I).—This 11-year-old boy, R. D., had an earache on the left side on April 18, 1940, not accompanied by any generalized respiratory infection. Two days later the left drum ruptured spontaneously with a small amount of discharge. There was only a little elevation of temperature the next day when the ear was further opened by a physician. There was then no change until the night before admission, at which time he suddenly had a chill and developed a temperature of 103° F. No chemotherapy had been given.

On admission, May 9, 1940, examination revealed a moderately acutely ill child with a temperature of 40 °C. The eardrums were intact but the left drum was full and red. The leucocyte count was 14,050 with a slight left shift. The x-rays showed destruction of the mastoid cells on both sides and an increase in density about the canal on the left side. A Tobey-Ayer test done shortly after

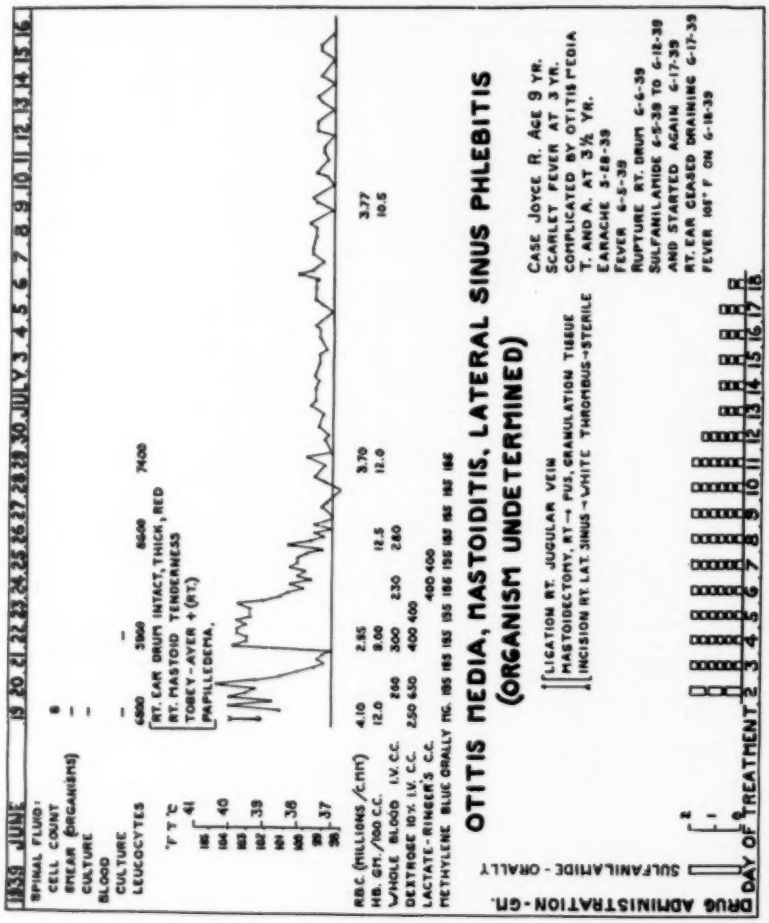


Chart 13.

entry showed a positive test on the left side. Blood culture made on May 9 was positive for hemolytic streptococci, and hemolytic streptococci were cultured from the ears. Treatment was begun with sulfanilamide given subcutaneously, and on the following day, May 10, ligation of the left jugular vein in the neck and left mastoidectomy were performed with incision of the left lateral sinus by Dr. A. J. Cone. Hemorrhagic, soft bone was found in the mastoid. The operation was brought rapidly to a close because of the critical condition of the patient. In addition to chemotherapy, supportive treatment in the form of whole blood transfusions, dextrose in 10 per cent solution, and lactate-Ringer's solution was given.

During the operation it was necessary to administer intravenous fluid, oxygen, and coramine. The sulfanilamide given for the next three days was mainly incorporated in the subcutaneous fluids.

Following operation the temperature subsided to normal within six days, and chemotherapy was discontinued. However, on May 22, the fourteenth day of treatment, the temperature was again elevated and during the next few days rose gradually until May 28, at which time there was a sharp rise to 39.5° C. Chemotherapy was resumed with oral doses of sulfanilamide, with, however, little effect on the temperature. On June 4 a probe was inserted into the lateral sinus and pus obtained. The temperature then remained practically normal until the end of the hospital stay. He was discharged on June 12 in good condition.

CASE 13 (Chart 13 and Table I).—This 9-year-old girl, J. R., complained of earache on May 28, 1939. On June 5 she began to have a low-grade fever, and the following day the right drum ruptured spontaneously and began to drain. In another hospital, x-rays and a blood culture were taken, a blood transfusion was given, and she was given sulfanilamide, the exact amount not being known. Drug therapy was discontinued on June 12 and resumed on June 17 because of continued temperature elevation. The ear had ceased draining by June 17, but the temperature was showing marked fluctuation with rises going to 105° F. on June 18.

She was admitted to the hospital here on June 19 with a temperature of 38.5° C., and appearing acutely ill, toxic and cyanotic. The right eardrum which was intact was, however, thick and red; there was tenderness over the right mastoid. There was papilledema of both discs and hemorrhages of the retinae. The leucocyte count was only 6,800 but with a marked left shift. A Tobey-Ayer test performed on the same day was positive on the right side. Chemotherapy was given as orally administered sulfanilamide. On June 20 the right jugular vein was tied off in the neck by Dr. Robert Votaw, and right mastoidectomy was done with incision of the lateral sinus. Pus and granulation tissue were found in the mastoid cells, and in the lateral sinus a white thrombus was found. No organisms were cultured from the operation site or from the blood, and the nature of the causative organism remained unknown. It is possible that the considerable amount of chemotherapy which the patient had received had sterilized the infection by the time of operation. This further emphasizes that while surgical treatment of such a condition is necessary, chemotherapy gives an added margin of safety by controlling the infection in large part. Recovery following the operation was very satisfactory with return of the temperature to normal on the sixth postoperative day.

Supportive treatment in the form of whole blood transfusions and dextrose and lactate-Ringer's solutions was given, as in the preceding cases. The cyanosis from methemoglobinemia sometimes became intense but was successfully controlled by methylene blue given orally.

CASE 14 (Chart 14 and Table I).—W. B., 4 years old, entered with a history of repeated previous attacks of tonsillitis and earache without drainage. On April 29, 1938, he began to complain of pain in the left ear. He was given treatment locally without chemotherapy for several days, and on May 7 the left drum ruptured spontaneously. On May 10 there was a sudden chill and a rise in temperature to 106° F. He became drowsy and complained of some stiffness of his neck.

On entry to the hospital on May 11 the initial examination revealed an acutely ill child with ptosis of the left eyelid, mild papilledema of both discs, lateral nystagmus on looking to left, suppurative otitis media on the left, and a

temperature of 38.6° C. There were no external signs of mastoiditis, but there was tenderness along the left mandible, and x-ray revealed greatly obscured cellular structure on the left side. The right side also showed some cloudiness. The leucocyte count was 25,400 with moderate left shift. A Tobey-Ayer test done on the day of admission was questionably positive on the left side. The temperature continued to be high and to show large daily fluctuations. The initial blood culture was positive for *Streptococcus viridans*. The patient was placed on chemotherapy, sulfanilamide given orally, and on May 13 a left mastoidectomy with

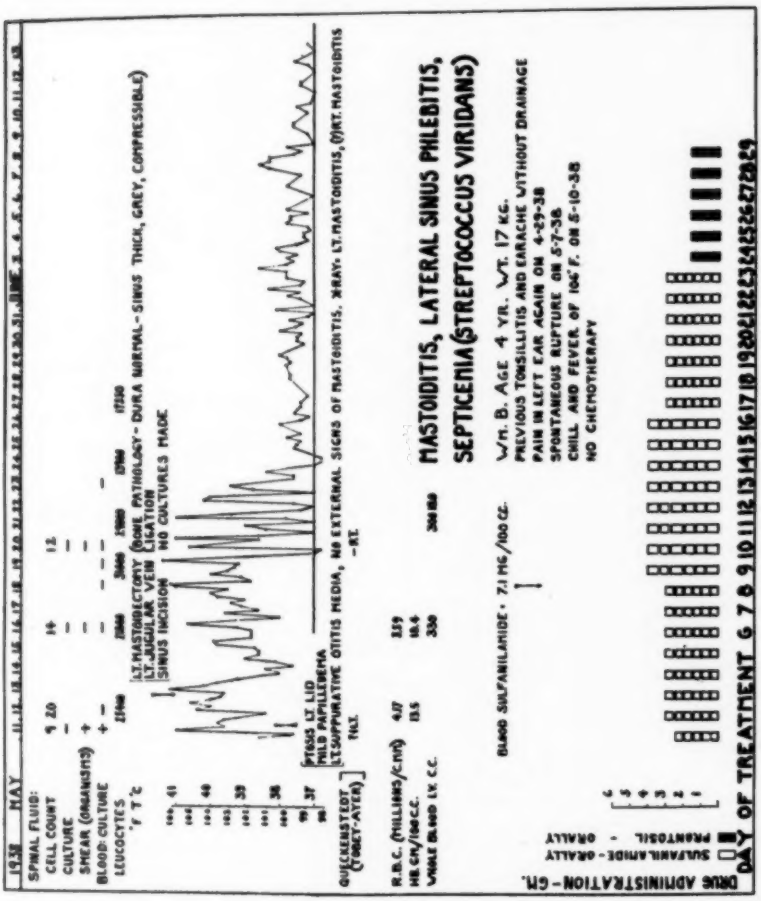

MASTOIDITIS, LATERAL SINUS PHLEBITIS, SEPTICEMIA (STREPTOCOCCUS VIRIDANS)
Wm. B. Age 4 yr., Wt. 17 kg.
Previous tonsillitis and earache without drainage
Pain in left ear again on 4-29-38
Spontaneous rupture on 5-7-38
Chill and fever of 106° F. on 5-10-38
No chemotherapy
DAY OF TREATMENT
DRUG ADMINISTRATION - GM.
SULFANIL AMIDE - ORALLY
PRONTOSIL - ORALLY

Chart 14.

ligation of the left jugular vein in the neck and incision of the lateral sinus was done by Dr. Robert Votaw. There was considerable bone pathology in the mastoid and a gray and thickened but compressible lateral sinus. The vein was not incised. No cultures were made from either mastoid or lateral sinus. The postoperative course was stormy with high septic temperature for eleven days and then subsidence to a low-grade elevation for the next two weeks. However, as

the general condition improved markedly in the latter period and blood cultures remained negative, chemotherapy was discontinued on June 8. The temperature then fell to normal and remained so. As in all other cases, the general care of the patient included whole blood transfusions and maintenance of proper fluid and electrolyte balance. He was discharged on June 13, 1939, in good condition except for a large defect over the mastoid due to the operative wound.

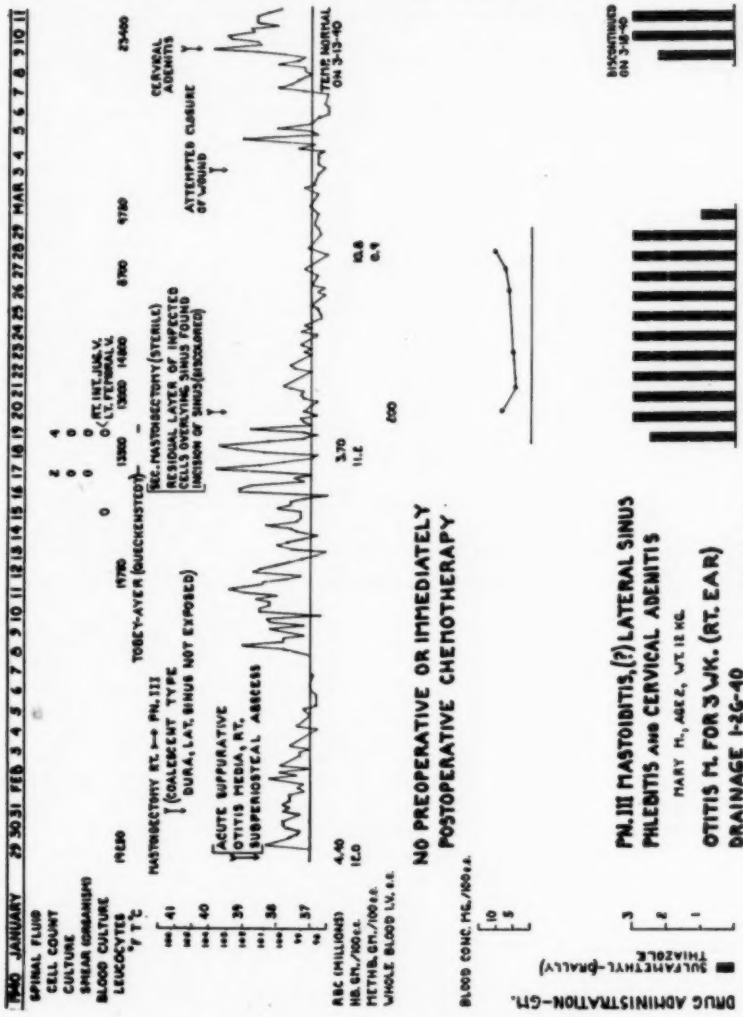

1940 JANUARY 29 30 31 FEB 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 MAR 3 4 5 6 7 8 9 10 11
SPINAL FLUID
CELL COUNT
CULTURE
SMEAR ORGANISMS
BLOOD CULTURE
LEUCOCYTES
MASTOIDECTOMY RT. → PN. III
[COALESCENT TYPE
DURA, LAT. SINUS NOT EXPOSED]
TOBEY-AYER (QUICKENSTEDT)
REC. MASTOIDECTOMY (STERILE)
[RESIDUAL LAYER OF INFECTED
CELLS OVERLYING SINUS FOUND
INCISION OF SINUS (UNCOAGULATED)
ATTEMPTED CLOSURE OF WOUND
CERVICAL ADENITIS
ACUTE SUPPURATIVE
OTITIS MEDIA, RT.
SUBPERIOSTEAL ABSCESS
TEMP. NORMAL ON 3-10-40
DISCONTINUED ON 3-10-40
NO PREOPERATIVE OR IMMEDIATELY
POSTOPERATIVE CHEMOTHERAPY
RBC (MILLIONS)
HB. GM./100 c.c.
METHB. GM./100 c.c.
WHOLE BLOOD LV. c.c.
BLOOD CONC. MG./100 c.c.
PN. III MASTOIDITIS, (?) LATERAL SINUS
PHLEBITIS AND CERVICAL ADENITIS
MARY M., AGE 2, WT. 12 KG.
OTITIS M. FOR 3 WK. (RT. EAR)
DRAINAGE 1-26-40
HOSPITAL DAY
DRUG ADMINISTRATION—GM.
SULFANILAMIDE (ORALLY)
THIAZOLE

Chart 15.

CASE 15 (Chart 15 and Table I).—This girl, M. M., was 2 years old on admission to the hospital. She had been well until three weeks previously when she complained of pain in the right ear. This was relieved at the time by local therapy. One week prior to entry she became fretful and again complained of pain in the

ear, and three days before entry the right eardrum ruptured spontaneously and drained. On this same day a swelling began to appear behind the right ear.

She was admitted to the hospital on Jan. 29, 1940, with a normal temperature but with signs of acute suppurative otitis media and a subperiosteal abscess on the right side. She was given no chemotherapy, and two days later a right mastoidectomy was performed by Dr. Lee Wallace Dean, Jr., and there was found a coalescent type of mastoiditis from which the pneumococcus type III was cultured. The dura and lateral sinus were not exposed. The postoperative course was uneventful for the first week, but then there developed a high septic type of temperature with large daily fluctuations. Acute otitis media was discovered on the left side, and myringotomy was done on that side on Feb. 16. After two more days of high spiking temperature, on the recommendation of the Department of Pediatrics, chemotherapy was begun on Feb. 19 with orally administered sulfamethylthiazole, and on Feb. 20 a second mastoidectomy on the right was done with incision of the lateral sinus by Dr. Guerdan Hardy. At this operation a residual layer of infected cells overlying the lateral sinus was found, and the sinus itself was discolored. Cultures made at this time were sterile, but a biopsy revealed lateral sinus phlebitis. The temperature had fallen promptly to normal before the operation with the institution of chemotherapy and remained so until March 4, the drug having been discontinued on Feb. 29. Then following attempted closure of the wound, there was again elevation of temperature which was due to the development of cervical adenitis. Chemotherapy was resumed with sulfamethylthiazole on that day and was continued until March 18, which was five days after the regaining of a normal temperature on March 13. Blood concentrations of between 5 and 10 mg. per 100 c.c. were obtained with sulfamethylthiazole administered by mouth.

A Tobey-Ayer test was performed just before the second mastoidectomy but was negative. Blood cultures taken at this time from the right internal jugular vein and left femoral vein simultaneously were both sterile.

Following the second course of chemotherapy the improvement was rapid, and she was discharged on March 19, 1940, in good condition.

CASE 16 (Chart 16 and Table I).—This 7-year-old girl, D. H., first developed otitis media when 4 months of age. The left ear seemed chiefly involved, and each winter there would be recurrences of pain and purulent drainage. About a month before admission she again complained of severe pain in her left ear and developed fever which persisted and was remittent in type. Two weeks later very severe frontal headache began and persisted, and a week before admission projectile vomiting, marked drowsiness, frequent shrill cry, a turning of her head and eyes to the right, and nystagmus developed and persisted. On admission on Feb. 22, 1940, all of the above-mentioned symptoms and signs were verified, and in addition there was noted severe dehydration, emaciation, and anemia. The left ear canal was filled with foul pus, discharging through multiple perforations in a greatly thickened drum. There were no external signs of mastoiditis. The right drum was also thick and gray, with a small dry perforation anteriorly. There was a slight, but definite, left facial paralysis. The original impression of Dr. Alfred Schwartz, who admitted her, was that she had left mastoiditis with probably a left cerebellar abscess, localized meningitis and possibly lateral sinus thrombosis, all of which later were found to be present. A diagnostic lumbar puncture revealed ground-glass appearing fluid containing approximately 1,000 cells but proving to be sterile on culture. The Tobey-Ayer test was frankly positive on the left. Dehydration was quickly relieved by fluid administration, and chemotherapy was started with intravenously administered sodium sulfamethylthiazole. X-ray revealed complete obliteration of the cellular structures

of the left mastoid and a well-defined area of rarefaction in the region overlying the knee of the lateral sinus, which was interpreted as being a large perisinus abscess. Cloudiness of the right mastoid was also present but with trabeculae still intact. The fundi were normal at this time.

As soon as the sterile character of the meningitis was determined and the patient well hydrated and with good concentration of sulfonamide, which was on

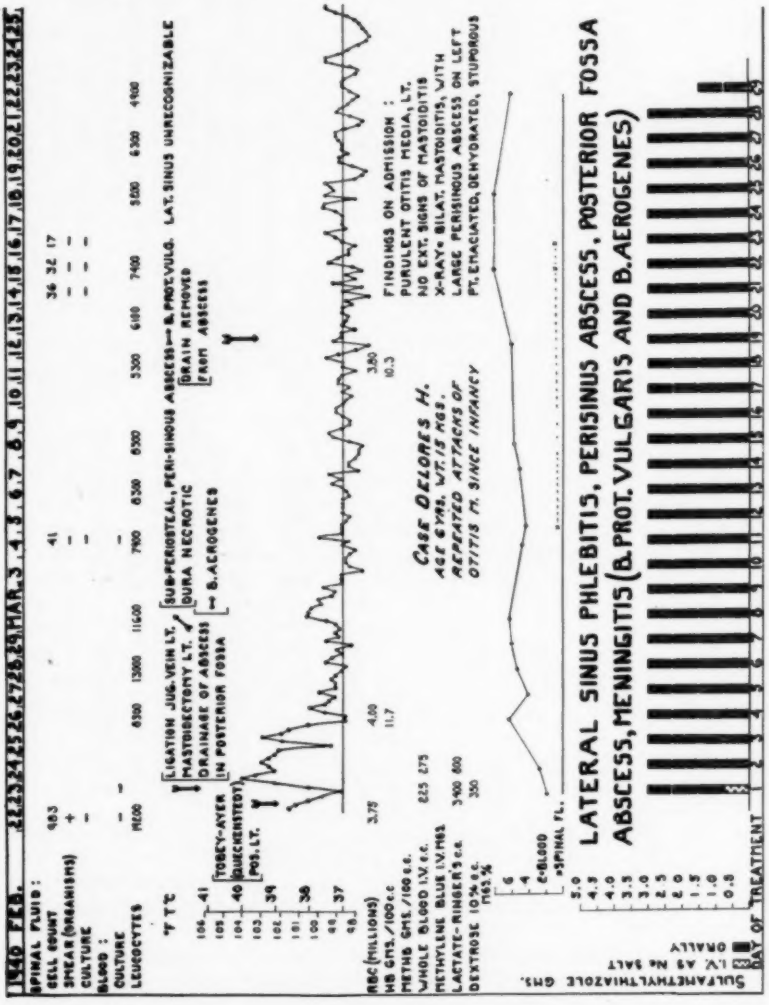

LATERAL SINUS PHLEBITIS, PERISINUS ABSCESS, POSTERIOR FOSSA ABSCESS, MENINGITIS (B. PROT. VULGARIS AND B. AEROGENES)
CASE OLLORES H.
AGE 6 YRS. WT. 15 LBS.
REPEATED ATTACKS OF OTITIS M. SINCE INFANCY
FINDINGS ON ADMISSION: PURULENT OTITIS MEDIA, L.T. NO EXT. SIGNS OF MASTOIDITIS X-RAY: BILAT. MASTOIDITIS, WITH LARGE PERISINUS ABSCESS ON LEFT PT. EMACIATED, DEHYDRATED, STUPOROUS
LIGATION JUG. VEIN L.T. MASTOIDECTOMY L.T. DRAINAGE OF ABSCESS IN POSTERIOR FOSSA
SUB-PERIOSTEAL, PERI-SINUS ABSCESS — B. PROT. VULG. DURA NECROTIC — B. AEROGENES
BRAIN REMOVED FROM ABSCESS
LAT. SINUS UNRECOGNIZABLE
TOBEY-AYER QUICKENSTEDT
POS. LT.
DAY OF TREATMENT
SULFANILAMIDE GMS. I.V. AS Na SALT ORALLY
SPINAL FL.
BLOOD
RBC (MILLIONS)
HB GMS./100 c.c.
METHB GMS./100 c.c.
WHOLE BLOOD I.V. c.c.
METHYLENE BLUE I.V. MGS.
LACTATE-RINGER'S c.c.
DEXTROSE 10% c.c.
LEUCOCYTES
CULTURE
BLOOD:
CULTURE
SMEAR (ORGANISMS)
CELL COUNT
SPINAL FLUID:

Chart 16.

the day following admission, mastoidectomy was performed by Dr. Robert Votaw, after ligation of the left jugular vein. A subperiosteal abscess was encountered with great destruction of bone which could be lifted out in pieces. There was some cholesteatoma present. The dura was thick and red. The lateral sinus was covered with granulations over a wide area and was very necrotic in appearance.

There was an area about the size of a dime where the bone overlying the sinus was gone. No normal-looking dura or sinus could be found, and in clearing out Troutman's triangle, a hole through the dura was encountered, through which about two ounces of foul greenish pus gushed. *Bacillus proteus* was cultured from

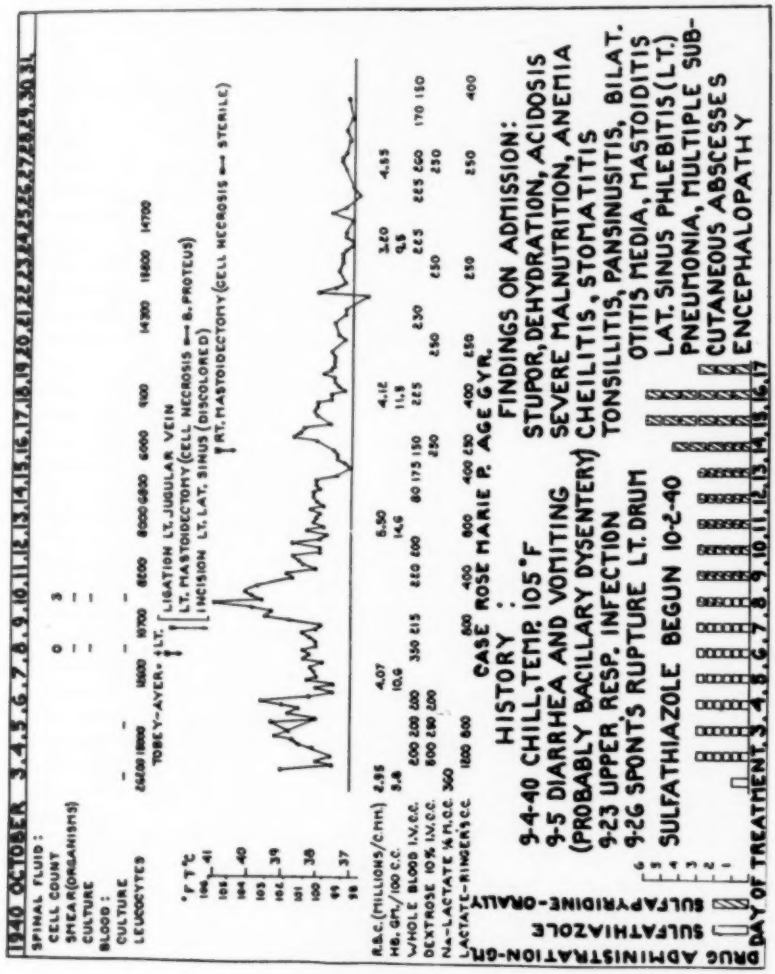


Chart 17.

the mastoid pus and *Bacillus aerogenes* from the brain abscess. Following this operation and with continued sulfamethylthiazole administration and supportive therapy, gradual improvement followed. Some mental obtuseness and abnormal behavior continued, however, and on March 14 bilateral papilledema was noted. Daily lumbar punctures were then made with diminution and then complete disappearance of the papilledema. Chemotherapy was discontinued on March 22. Shortly afterward headache and papilledema recurred, and because of these findings and the persistence of some increase in spinal fluid cell count, a re-

exploration of the mastoid was done on March 30. Some tissue thought to be sinus, which was yellow and softer than the surrounding dura, was removed and found to be necrotic brain tissue. Two days later, because of increase in spinal fluid cell count to approximately 2,000, chemotherapy was resumed, this time with sulfapyridine. Although the spinal fluid again proved to be sterile and the cell count again dropped, the patient became more and more stuporous and with increasing papilledema and soon had to be given fluid by the continuous intravenous injection method. Some cerebellar herniation developed, and frequent lumbar punctures were again made to reduce pressure. On April 17 a pneumoencephalogram showed marked internal hydrocephalus. Daily lumbar punctures were continued and on May 21 diathermy was used to reduce the herniation, and gradually the wound could be closed. The patient was discharged from the hospital on July 5 and returned to school the next fall, and when examined on Oct. 29, 1940, seemed perfectly well.

CASE 17 (Chart 17 and Table I).—This 6-year-old girl, R. M. P., became ill on Sept. 4, 1940, with what was probably acute bacillary dysentery. She was very ill with this infection which was complicated by the development of a generalized upper respiratory infection on Sept. 23. Three days later the left eardrum ruptured spontaneously. She coughed considerably, ate very poorly, continued to have diarrhea, lost much weight and strength, and finally became stuporous. During the twenty-four hours prior to admission on Oct. 3, she received 3 Gm. of sulfathiazole.

On admission she was found to be stuporous, dehydrated, acidotic, severely malnourished, and anemic, with cheilitis, stomatitis, tonsillitis, pansinusitis, bilateral purulent otitis media, bilateral mastoiditis of the coalescent type, bronchopneumonia, and large subcutaneous abscesses. The latter contained staphylococcus pus and originated at the sites of subcutaneous fluid given more than a week before admission to the hospital. The acidosis and dehydration were immediately relieved by administration of ⅙ M.* sodium r-lactate and lactate-Ringer's and dextrose solutions, and the anemia by whole citrated blood transfusions. Chemotherapy was started immediately with sulfathiazole in a dosage of slightly more than 0.25 Gm. per kilogram per twenty-four hours. On Oct. 8, the sixth day of sulfonamide therapy, the Tobey-Ayer test was found positive on the left, and on the following day the left jugular vein was ligated in the neck by Dr. A. J. Cone, a left simple mastoidectomy performed, with necrotic pus-filled cells being found, and the lateral sinus which was found discolored was incised. *Bacillus proteus* grew from the mastoid culture. Sulfapyridine was then substituted for sulfathiazole after considerable postoperative temperature rise, following which the temperature fell almost to normal. On Oct. 16, the fourteenth day of sulfonamide treatment, a right simple mastoidectomy was done, cells being found necrotic but sterile on culture. After this the temperature remained normal and the patient gradually improved with the aid of repeated administration of whole citrated blood and of dextrose and lactate-Ringer's solution, and vitamins, especially of the B complex. On Oct. 18 a severe convulsion occurred which began on the left side and spread to the right. The following day a right-sided hemiparesis was noted which subsequently gradually improved. On Dec. 19 pus was aspirated from both maxillary antra, and the sinuses later were irrigated by way of treatment until the washings returned clear. On Feb. 2, 1941, a severe convulsion occurred which began on the right side and later spread to the left. The spinal fluid at that time was normal. An electroencephalogram made a month later suggested a lesion in the left tempero-occipital region. Convulsions recurred at approximately biweekly intervals. On March 13, a pneumoencephalogram

*Molar.

showed changes suggestive of a degenerative lesion in the posterior part of the left cerebral hemisphere. At no time was definite papilledema noted.

CASE 18 (Chart 18 and Table I).—This 25-month-old girl, G. E., when 9 months of age, developed otitis media in one ear, which one was not remembered by the mother, with drainage lasting for three months. Five days before admission to

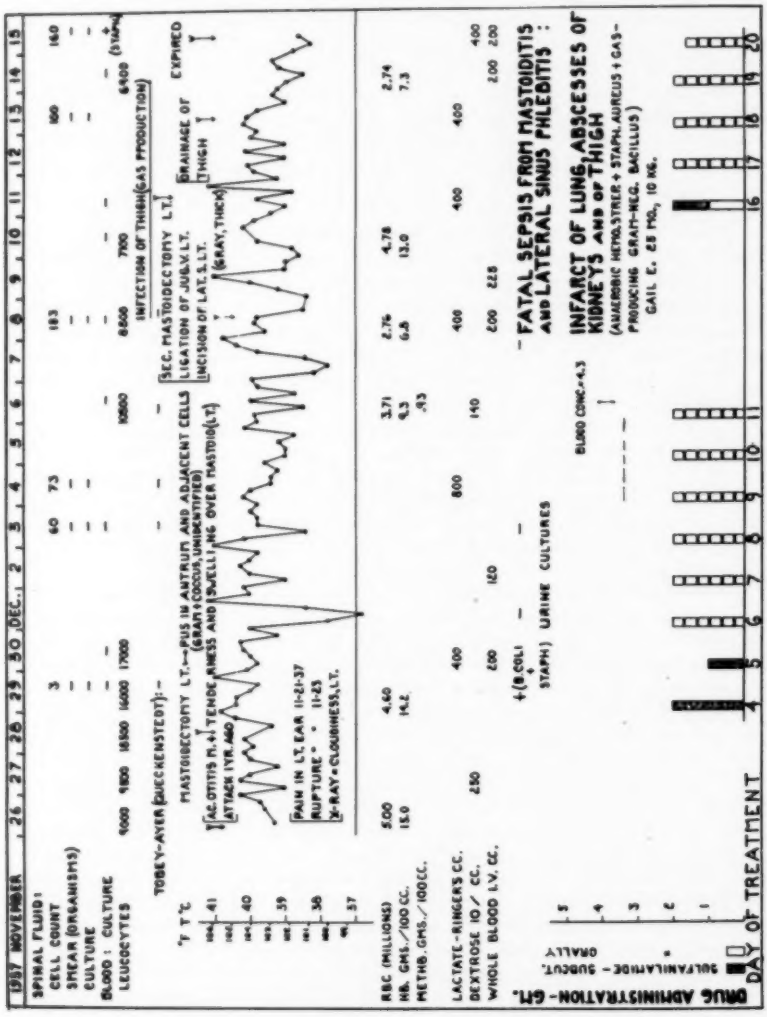

1937 NOVEMBER 26 27 28 29 30 DEC. 2 3 4 5 6 7 8 9 10 11 12 13 14 15
SPINAL FLUID:
CELL COUNT 3 60 73 183 150 140
SMEAR (ORGANISMS) — — — — — —
CULTURE — — — — — —
BLOOD: CULTURE — — — — — — — (STAPH)
LEUCOCYTES 9000 9800 18500 16000 17000 10500 8500 7500 6400
INFECTION OF THIGH (GAS PRODUCTION)
TOBEY-AYER (BUCKENSTEDT):—
SEC. MASTOIDECTOMY LT.
°F T °C
MASTOIDECTOMY LT.—PUS IN ANTRUM AND ADJACENT CELLS (GRAM + COCCUS, UNIDENTIFIED)
LIGATION OF JUG.V.LT.
DRAINAGE OF THIGH
EXPIRED
AC. OTITIS M. & TENDERNESS AND SWELLING OVER MASTOID (LT)
INCISION OF LAT. S. LT.
ATTACK (1YR. AGO)
X-RAY, THIGH
PAIN IN LT. EAR 11-21-37
RUPTURE " " 11-23
X-RAY + CLOUDINESS, LT.
RBC (MILLIONS) 5.00 4.60 3.71 2.76 4.78 2.74
HB. GMS./100 CC. 15.0 14.2 9.3 6.8 13.0 7.3
METHB. GMS./100 CC. .93
LACTATE-RINGER'S CC. 400 800 400 400 400
DEXTROSE 10% CC. 250 200 120 140 200 225 200 200
WHOLE BLOOD I.V. CC. 400
+(B.COLI + STAPH) — — — URINE CULTURES
- FATAL SEPSIS FROM MASTOIDITIS AND LATERAL SINUS PHLEBITIS:
INFARCT OF LUNG, ABSCESSES OF KIDNEYS AND OF THIGH
(ANAEROBIC HEMOLYTIC STREP. + STAPH. AUREUS + GAS-PRODUCING GRAM-NEG. BACILLUS)
GAIL E. 25 MO., 10 KG.
BLOOD CONC.=4.3
DRUG ADMINISTRATION-GM.
SULFANILAMIDE - SUBCUT. ORALLY
DAY OF TREATMENT
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Chart 18.

the hospital she developed pain in her left ear, and two days later spontaneous rupture of the left drum occurred. The following day some swelling behind the ear was noted, and the temperature reached 104° F. On admission on Nov. 26, 1937, purulent otitis media on the left was found, culture from the pus showing *Staphylococcus aureus*. There were also tenderness and swelling over the mastoid.

On x-ray the cellular structures were found hazy. On Nov. 28, mastoidectomy was done by Dr. L. W. Dean, Jr., and pus under pressure was noted in the cells, the culture of which showed a large gram-positive coccus, and a single colony of a green streptococcus. The sinus plate seemed normal and was left. The next day a catheterized specimen of urine contained a few leucocytes but contained *Bacillus coli* and *Staph. aureus* on culture. Sulfanilamide therapy was begun at this time. No improvement followed the operation or the institution of chemotherapy. On Nov. 30 signs of pneumonia were noted in the right lower lobe. Some cervical adenitis developed. The Tobey-Ayer tests continued to be negative with normal spinal fluid findings. Otitis media developed on the right side, and on Dec. 7 myringotomy revealed pus from which an unidentified pneumococcus was grown. On Dec. 9 the left mastoid was reopened, the sinus plate removed, and the sinus found white, thickened, and covered with a thick pyogenic membrane from the bulb to the knee. It was still compressible. The jugular vein was then ligated in the neck, and then the lateral sinus was incised through the worst looking portion. The picture of sepsis continued, and on Dec. 10 a swelling of the soft tissue of the right thigh was noted which, the following day, was seen to contain gas on x-ray examination. Twenty cubic centimeters of polyvalent gas gangrene antitoxin were then given intramuscularly. On Dec. 13 the thigh was drained, and a large abscess pocket was found extending along the femur. From this pus, Dr. Louis Julianelle isolated an anaerobic hemolytic streptococcus, an unidentified gram-negative gas-producing bacillus, and a nonmannite fermenting staphylococcus. Death occurred on Dec. 15, on which day a staphylococcus was grown from the blood, the first positive blood culture.

At autopsy a hemolytic *Staph. aureus* was grown from the heart's blood, mastoid and thigh. A thrombus was found in the lower branch of the right pulmonary artery with infarction of the right lower lobe. Embolic abscesses were seen in both kidneys. Permission was not granted for examination of the brain.

CASE 19 (Chart 19 and Table I).—This 7-year-old boy, J. I., developed pain in his left ear on Dec. 7, 1937, during the course of an upper respiratory infection. The earache had barely subsided when, on Dec. 13, he developed measles. On Dec. 19, after recurrence of pain, the left drum ruptured spontaneously. He was admitted to the hospital the following day where it was noted that, in addition to purulent otitis media, there was cellulitis with much edema involving the face, neck, and scalp surrounding the affected ear. There was also evidence of acute pansinusitis. Cultures from the draining ear, from the scalp infection, from the nasopharynx, and from the blood showed a streptococcus, which at first produced greenish colonies with but slight hemolysis. Later the organism from the blood and from the lateral sinus seemed more typically a β hemolytic streptococcus. On Dec. 22 signs of pneumonitis developed in the right lower lobe, and the scalp infection was drained. X-ray of the mastoid showed hazy, poorly defined trabeculae on the left; of the sinuses, complete opacity of the maxillary antra; and of the chest, questionable early bronchopneumonia. Despite drainage of the scalp infection, sulfanilamide administration, transfusions, and fluid administrations, the picture of sepsis continued and the blood cultures remained positive. On Dec. 26 the Tobey-Ayer test was found frankly positive on the left, and bilateral papilledema with retinal hemorrhages was noted. The next day the left internal jugular vein was ligated by Dr. Arthur M. Alden at the usual site in the neck. It seemed normal. Mastoidectomy was then done, and a coalescent type of mastoiditis was found. The lateral sinus was thrombosed over a considerable length and was incised until free bleeding was obtained posteriorly. No improvement followed this operation despite continued sulfanilamide administration and supportive therapy in the form of blood transfusions, dextrose and lactate-Ringer's

administration, and methylene blue, which was frequently necessary to control methemoglobinemia. Blood cultures continued to be positive. On Jan. 1, 1938, ulceration of the helix of the right auricle was noted, and the next day an abscess formed over the sacrum. At this time purulent drainage was also noted coming from the neck wound where the jugular vein was ligated. Central nervous system symptoms, including bilateral ankle clonus, Kernig's signs, and nuchal rigidity, lateral nystagmus, and diplopia then developed and prompted diagnostic lumbar

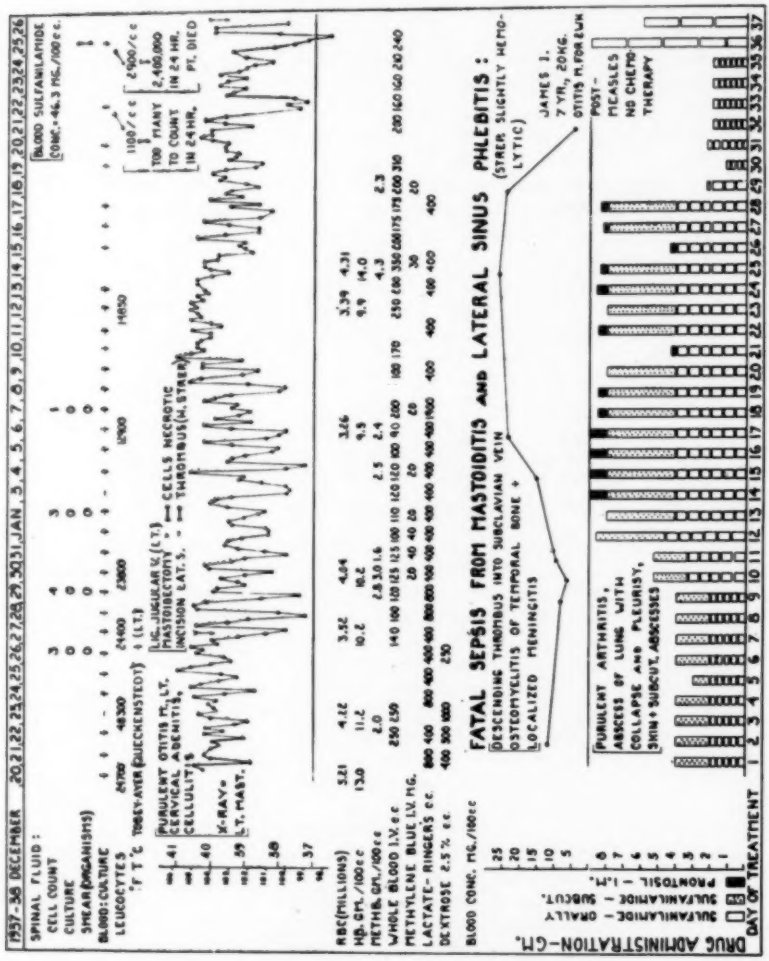


Chart 19.

puncture. The spinal fluid was found normal, however. Prontosil was then administered in addition to sulfanilamide, but no improvement followed. On Jan. 6 the neck was reopened and the jugular vein, together with some enlarged glands, was excised from the point of ligation to the angle of the jaw. A small undrained pocket of pus was found at the site of the ligation. After this the patient did even less well; the mastoid and neck wounds continued to drain profusely, and

numerous skin ulcers appeared which showed no tendency to heal. Swelling of the left shoulder region developed with dilated superficial veins. Later edema of the whole left upper extremity was noted, and venous obstruction was suspected. Considerable bleeding then occurred, particularly from the neck wound. Signs of pulmonary involvement continued, and on Jan. 26, shortly before death, thoracentesis yielded some 200 c.c. of dark, thin fluid from which hemolytic streptococci grew. The sulfanilamide content of this fluid was 40 mg. per 100 c.c. The spinal fluid at this time was xanthochromic but contained only 13 cells per cubic millimeter.

On Jan. 20 1 c.c. of citrated blood, cultured immediately, showed 1,100 colonies. One-tenth of a cubic centimeter after twenty-four hours' incubation showed too many colonies to count. On Jan. 26 the blood as drawn showed 2,900 colonies per cubic centimeter, and after twenty-four hours' incubation, 2,400,000, despite a sulfanilamide concentration of 46.3 mg. per 100 c.c.

At post-mortem Dr. H. McCordock found (1) extension of the infection of the left jugular vein into the axillary vein, with an occluding thrombus there; (2) an abscess of the right lower lobe of the lung, with fibrinous pleurisy and bronchopneumonia of the remainder of the lower lobe and of the middle lobe; (3) localized meningitis over the inferior surface of the left temporal lobe, with adjacent osteomyelitis of the temporal bone; (4) numerous subcutaneous abscesses; and (5) purulent arthritis of the left sternoclavicular and shoulder joints.

From the heart's blood grew a slightly hemolytic streptococcus.

Temporal bone studies made by one of us (D. W.) revealed the following: A mild otitis media and mastoiditis were found in the right ear upon microscopic post-mortem examination. An anatomic variation was observed in that the malleo-incudal joint and drum membrane were relatively inferiorly placed. In the left ear, which was the one operated upon, the surgical wound was clean and free from pus. A very delicate empyemic membrane lined it and filled in the remaining pneumatic cells, the aditus ad antrum, and the posterior half of the middle ear cavity. Malleo-incudal joint lay embedded in this membrane as did the posterior crus of the stapes. The hypotympanic cells were filled with it. Although practically no pus cells were seen, it was evident that an active osteitis was still in progress at the time of death. The bony trabeculae at the upper level of the mastoid were abnormally irregular in contour and new bone was being laid down. The bone bordering the cranial cavity had jagged edges in many places. In the region of the jugular bulb the bone had a moth-eaten appearance, and multiple fistulous paths led toward the fossa in which a well-organized thrombus lay.

The inner ears on both sides exhibited atrophic organs of Corti and vestibular end-organs of the type of degeneration usually seen in cachexia. It is believed that the chemical nature of the endolymph becomes so altered that the end-organs practically go into solution, but there is never any evidence of fragmentation of cells as in autolytic degeneration.

DISCUSSION

I. Incidence.—As in our previous cases, boys outnumbered the girls, and the period of highest incidence was from 5 to 9 years of age. The absence of cases in 1941 coincides with a marked reduction in the incidence of operated mastoids, which in turn seems probably due to the more widespread use of sulfonamide drugs in the treatment of acute upper respiratory infections, and especially otitis media.

II. Etiology.—As in all previous studies of the etiology of lateral sinus phlebitis, the hemolytic streptococcus was by far the most frequently encountered organism, as may be noted from Table I.

There are a number of possible routes of extension to the lateral sinus from an infection in the temporal bone. As Ruskin has said, "The temporal bone lies in a venous bed." The superior lateral sinus borders the medial angle of the bone, following along the attachment of the tentorium. It connects the cavernous sinus with the upper end of the sigmoid sinus. The inferior petrosal descends from the cavernous sinus through Dorello's canal (in which also lies the sixth nerve) to join the jugular bulb. The cavernous sinus is further linked with the jugular bulb by the tortuous pericarotid venous plexus. Any one or all of these venous channels are subject to vascular and direct extension from the ears.

Fig. 1 illustrates vividly direct extension to the sigmoid sinus from infected mastoid cells in a case of pneumococcus type III infection. The patient was hospitalized before sulfonamide drugs were developed. Following a simple mastoidectomy the patient suffered with headache for nine weeks. At this time a second mastoidectomy was done. Postmortem examination of serial sections of the temporal bone showed that the routes of extension intracranialward were multiple. Not only this extension to the sinus occurred, but a purulent labyrinthitis was present, angle cells showed erosion intracranialward, and infection from the Eustachian tube had eroded into the carotid sheath.

Fig. 2 illustrates a pathologic dehiscence into the jugular bulb region through the floor of the middle ear cavity. This was in a case of *Streptococcus hemolyticus* in a 4-year-old child. Here again multiple routes of extension were present. Fig. 3 illustrates a thrombus in the pericarotid venous plexus. In addition to this, abscesses from the submucosa of the Eustachian tube were draining into the marrow of the petrous apex.

Pathologic routes similar to these could be traced microscopically in twelve cases studied post mortem by one of us (D. W.). Five of these were adults. All were postoperative patients except two. The extension occurred at the operative site in five of the ten operated cases. At operation the sinus appeared normal in this region in three cases. Ligation of the jugular was done in three cases.

The organisms found in these cases of lateral sinus thrombosis varied. Four were *Streptococcus hemolyticus,* three were pneumococcus III, two were *Bacillus influenzae,* and three staphylococcus.

III. Diagnosis.—As in our previous cases, involvement of the sinus occurred within the first two months of otitis media in the great majority of cases (fifteen of nineteen). Of considerable assistance in diagnosis was the fact that in nine cases purulent otitis media was unilateral, and in only two instances bilateral. In eight instances both

eardrums were found intact when first examined; in the majority of these, however, the history of previous purulent drainage pointed correctly to the more seriously involved side. In three cases the subperiosteal type of mastoiditis was present on the side of the phlebitis, and in twelve other cases, despite the absence of external evidence of mastoiditis, the x-ray indicated correctly the presence of mastoiditis on at least one side. In three cases there were neither external signs nor

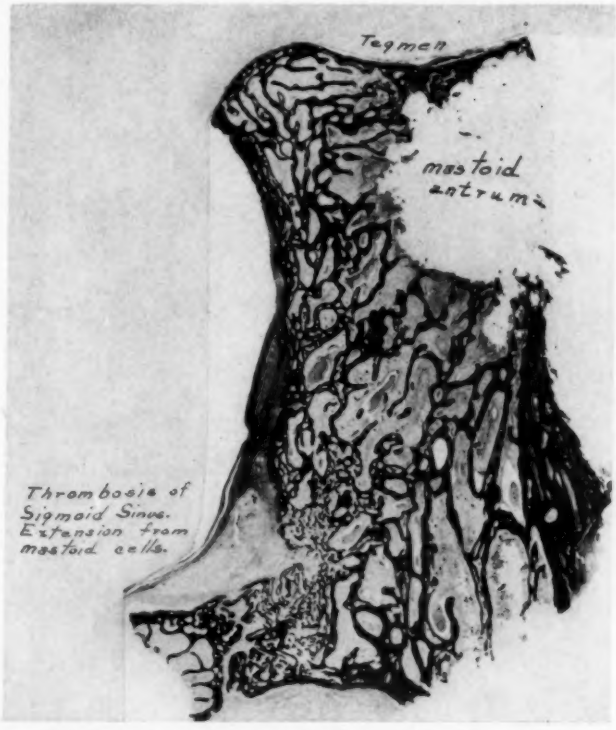


Fig. 1.—Adult male, 37 years of age. Vertical section through the mastoid of a pneumococcus type III otitis and meningitis. Note the direct extension from infected mastoid cells to the thrombosed sigmoid sinus. Multiple routes of extension were present in this case. Two mastoid operations were performed. The patient was hospitalized in 1931 prior to the time of chemotherapy.

clear-cut x-ray evidence of mastoiditis on either side, and in five cases it was eventually determined that the sinus was involved on the side opposite to that at first suspected from the ear history and findings and the x-rays of the mastoids. In these cases the Tobey-Ayer test was the determining factor in the making of the correct diagnosis. In fifteen of the nineteen cases this test was positive when first made, and in two other cases it became positive after an initial negative response. In the other two cases it remained persistently negative.

Fig. 2.—A vertical section through the right temporal bone in a case of streptococcus otitis media and meningitis. Note the pathologic dehiscence from the floor of the infected middle ear cavity into the jugular fossa. This 4-year-old boy was sick only ten days. Multiple abscesses were found throughout the petrosa, even in the tensor tympani muscle.

Fig. 3.—A section through the apex of the same streptococcus case illustrated in Fig. 2. Here an infected thrombus is seen in the pericarotid venous plexus. The presence of blood in the internal carotid artery gives evidence of some vascular obstruction in the arterial system.

Anatomically the human lateral sinuses are subject to variations in size and course. Whether these variations are related to racial differences is not known. Statistics compiled in Europe and in this country vary considerably. All agree that the right lateral sinus is more frequently larger than the left. Whether this bears any relationship to the greater frequency of otitis reported in the right ear is not known. Rudinger[2] (quoted from Piersol) found that bilateral symmetry occurred in 3 per cent of his cases; the left lateral sinus was larger in 27 per cent of the cases, and the right lateral sinus was larger in 70 per cent of the cases. These statistics come from central Europe. Woodhall[3] studied 100 cases at autopsy in Baltimore. He found bilateral symmetry in 48 per cent of the cases; the left lateral sinus was larger in 13 per cent of the cases; the right lateral sinus was larger in 39 per cent of the cases. Observations were made at fifty-nine autopsies in the Washington University Medical School by one of us (D. W.). In this group, fifty-four belonged to the white race; five were Negroes. There were forty-two male and seventeen female individuals. Both races and both sexes fell in each classified group and with no demonstrable significance of distribution. Bilateral symmetry was observed in 27.1 per cent of the cases; the right lateral sinus was larger in 54.2 per cent of the cases, and the left was larger in 18.7 per cent of the cases.

Numerous anomalies of the lateral sinuses have been reported in the literature.[6-12] A very large mastoid emissary vein may be present, carrying most or all of the blood outside of the skull before it reaches the sigmoid portion of the lateral sinus. The blood from the horizontal portion may pass over the tegmen of the petrosa as a persistent petrosquamosal sinus and empty through the foramen spurium (normally present only in the young infant). (This foramen is found in adult monkeys and carries about one-third of the blood from the horizontal portion of the lateral sinus.) The blood may continue more anteriorly and pass out of the skull through the foramen spinosum.

Woodhall[4] found anomalies of sufficient degree to alter readings in the Queckenstedt (Tobey-Ayer) test in 4 per cent of the cases. Four anomalies reported of congenital lack of a lateral sinus all occurred on the right side. This is interesting in view of the fact that the left lateral sinus is more frequently smaller. Ersner and Myers stressed the necessity for x-rays of the jugular bulb region.[5]

The importance especially of ruling out pneumonia as a cause for symptoms suspected of being due to lateral sinus involvement is well illustrated in Cases 20 and 21 (Charts 20 and 21) as is also the remarkable effect which sulfonamide treatment has on the pneumonic process. Recently we had difficulty for a few days in ruling out lateral sinus thrombosis in an infant 20 months of age with a history of previous purulent otitis media, who later developed an unexplained septic type of fever and on whom a Tobey-Ayer test was found positive on the left

side. After some forty-eight hours of incubation the blood culture grew out a Vi. strain of typhoid bacilli, and the course subsequently was typical of that of typhoid fever in an infant.

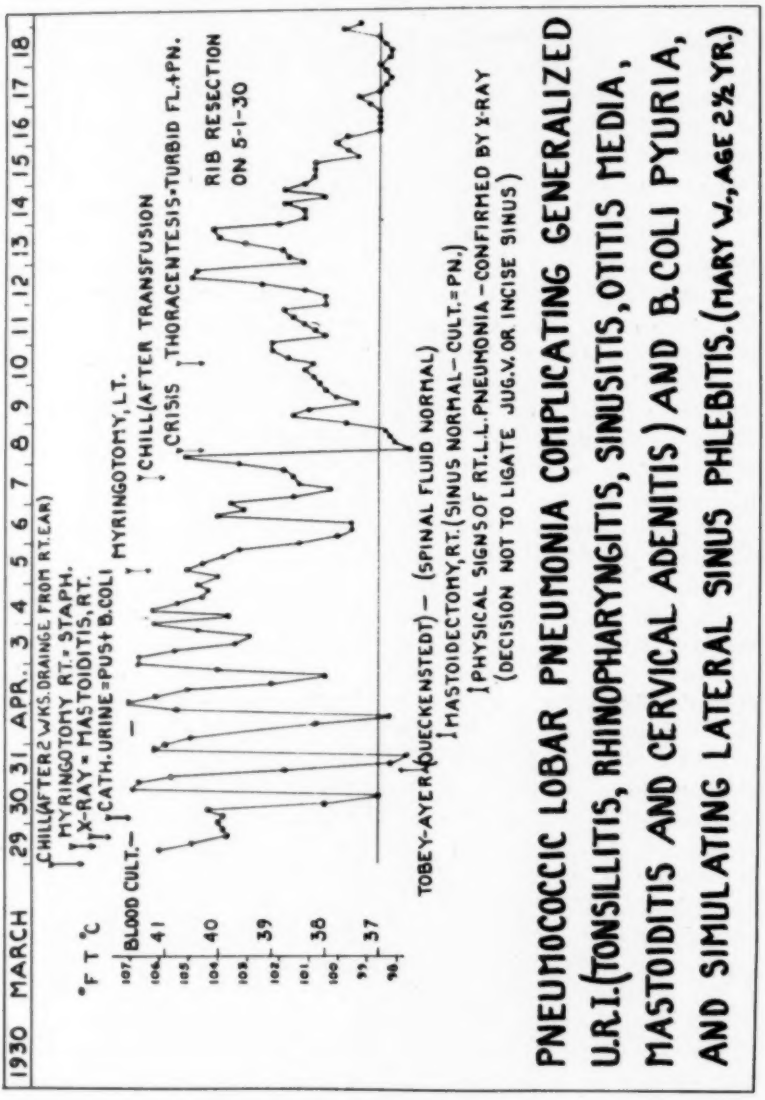

1930 MARCH 29 30 31 APR. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
CHILL(AFTER 2 WKS. DRAINGE FROM RT. EAR)
MYRINGOTOMY RT. = STAPH.
X-RAY = MASTOIDITIS, RT.
CATH. URINE = PUS + B. COLI
MYRINGOTOMY, L.T.
CHILL(AFTER TRANSFUSION
CRISIS
THORACENTESIS-TURBID FL.+PN.
RIB RESECTION ON 5-1-30
°F T °C
BLOOD CULT.—
107 41 106 105 40 104 103 39 102 101 38 100 99 37 98
TOBEY-AYER-QUECKENSTEDT) — (SPINAL FLUID NORMAL)
MASTOIDECTOMY, RT. (SINUS NORMAL — CULT. = PN.)
PHYSICAL SIGNS OF RT. L.L. PNEUMONIA — CONFIRMED BY X-RAY
(DECISION NOT TO LIGATE JUG. V. OR INCISE SINUS)
PNEUMOCOCCIC LOBAR PNEUMONIA COMPLICATING GENERALIZED U.R.I. (TONSILLITIS, RHINOPHARYNGITIS, SINUSITIS, OTITIS MEDIA, MASTOIDITIS AND CERVICAL ADENITIS) AND B. COLI PYURIA, AND SIMULATING LATERAL SINUS PHLEBITIS. (MARY W., AGE 2½ YR.)

Chart 20.

Factors other than such anatomic anomalies may also keep the Tobey-Ayer test from being foolproof, as pointed out previously,[1] and if its results are not clear-cut and in keeping with the general clinical picture,

it should certainly be repeated (under anesthesia if necessary), and all of the possible reasons for false-positive and false-negative results should be carefully considered. Even after such precautions are taken, one should expect occasionally both to fail to find thrombosis and to over-

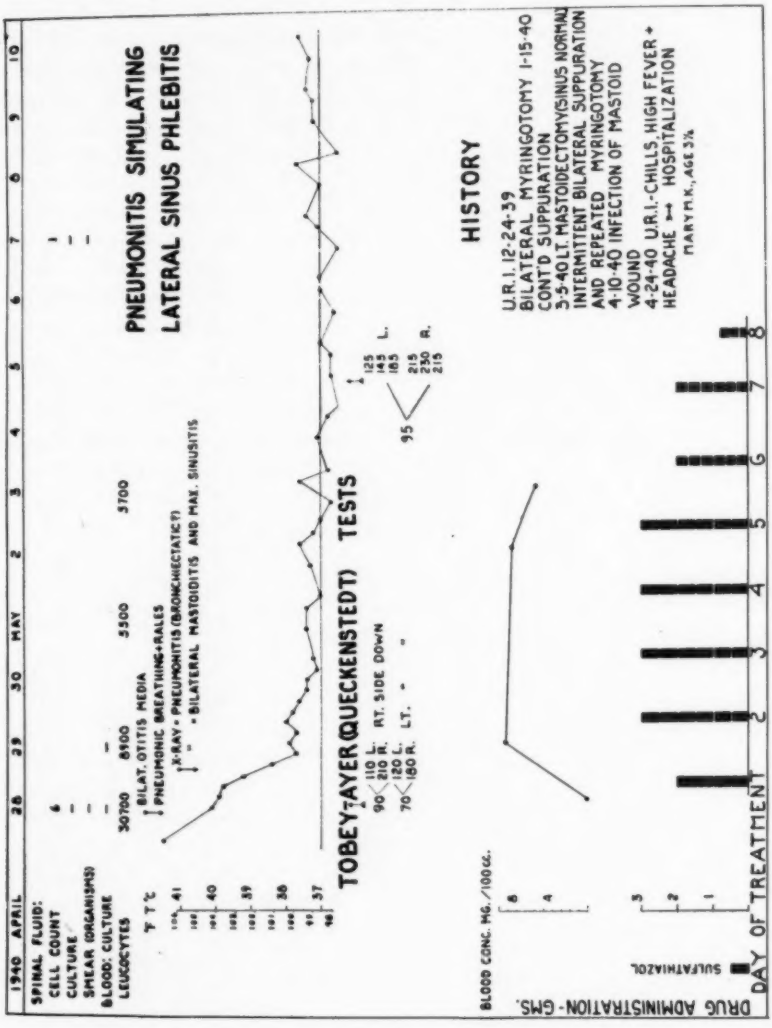


Chart 21.

look its presence, especially if it is an incomplete or mural thrombus. With the protection that sulfonamide chemotherapy affords, it would seem wiser to risk the former error rather than leave an infected vein undrained.

In ten cases the initial blood culture was positive, in two more subsequent cultures became positive, while in the remaining seven cases cultures were negative, single cultures in two instances, and repeated cultures in two others; in one case there were three persistently negative cultures, and in the two others, four.

The failure to find in every instance the classical signs of lateral sinus thrombosis, (1) external evidence of coalescent mastoiditis, (2) complete venous block on one side only, and (3) persistent bacteremia, which would make the recognition and localization of lateral sinus involvement easy, is not, in our opinion, to be attributed to any great extent to a so-called "masking" effect of sulfonamides. We emphasized the commonness of "masked" mastoiditis in our previous paper, and in our present series, of the three cases without external evidence of mastoiditis and without clear-cut x-ray findings, two patients (Cases 2 and 11) had not had previous chemotherapy, and in Case 7 the drug administered had been so small in amount and so shortly before admission as to be of doubtful significance from this point of view. In Cases 4, 5, 9, and 13, receiving chemotherapy in much the same manner, there was no unusual "masking." If we all would but accept and remember the teachings of L. W. Dean, Sr., that "every case of otitis media is potentially a case of mastoiditis, and every case of mastoiditis is potentially a case of lateral sinus phlebitis and one cannot always be certain of what may or may not be in a mastoid without operative inspection," made long before the discovery of the value of sulfonamide drugs, we would not regard too seriously any possible "masking" effect of sulfonamide chemotherapy and would learn to diagnose types of mastoid involvement other than the coalescent subperiosteal variety.

IV. Pathologic Findings (At Operation or Post Mortem).—As in our previous cases, the pathologic changes in the mastoid varied from the acute hemorrhagic type to the sclerotic not only in different subjects but in different parts of the same mastoid. It should specially be noted that from the ten mastoids specifically cultured at the time of operation, organisms were recovered from seven, despite usually sufficient chemotherapy to abolish bacteremia. Much the same variation as previously noted in sinus pathology was also found, and from eight cultures, organisms were grown in five, only two being associated with positive mastoid cultures. A similar situation was noted in the two fatal cases (18 and 19). Of the nine cases without positive cultures from mastoid or sinus, *no* cultures were made in four, while in three others only one of the two sites was cultured.

The persistence of viable organisms in the undrained necrotic mastoid cells and in the thrombosed sinus is in marked contrast to the rapidity with which bacteremia was abolished after institution of chemotherapy. In the twelve cases with positive blood cultures, bacteremia was abolished preoperatively in all instances but two (Cases 7 and 19). In another

patient (Case 9) operated on the third day of chemotherapy, the blood culture became positive immediately following operation but was negative again the following day.

In the patient in Case 11 the spinal fluid had also become sterile before operation, as was true in all of our operated cases of hemolytic streptococcal meningitis, to be reported later.

V. Clinical Courses of Operated Cases and Results.—In our previous patients receiving no sulfonamide drug, the gross mortality rate was twenty-one of sixty, or 35 per cent, and with the exclusion of the unoperated cases and those moribund at the time of operation, it was 27.8 per cent. There was also a high incidence of metastatic infection not associated with a fatal outcome. In the present series of sulfonamide treated cases, there were two deaths and seventeen recoveries, a mortality rate of 10.5 per cent.* One of the fatalities (Case 18) was a mixed infection with gas gangrene, all the organisms involved apparently being unaffected by the one drug, sulfanilamide, then available. In the other fatality (Case 19) the streptococcal infection followed shortly after measles, and the patient apparently had unusually little resistance to it. Extension of the infected thrombus in the internal jugular vein continued to descend into the axillary vein and led to a persistent and very heavy blood stream infection. Very high concentrations of sulfanilamide (46 mg. per 100 c.c.) failed to sterilize the blood stream or to prevent continued multiplication or organisms in drawn blood.

On the other hand, all the other cases had what was noted in twenty-two, or approximately only one-third, of the sixty earlier cases, namely, uncomplicated, quick, or only slightly delayed postoperative recoveries from the septic manifestations. Among them were one case of generalized hemolytic streptococcal meningitis, one case of sterile meningitis, one brain abscess which drained quite satisfactorily through the mastoid wound, two cases of arthritis (one definitely purulent), and three cases of pneumonitis.

Those patients showing slightly protracted courses (Cases 4, 7, 10, 12 and 15) were given either considerably less drug than we would now administer or had the drug administration discontinued too soon.

SUMMARY AND CONCLUSIONS

The addition of sulfonamide chemotherapy to the management of sepsis from lateral sinus phlebitis during the past five years has greatly

*Since this paper was written, another patient was successfully treated with sulfadiazine, mastoidectomy, jugular vein ligation, and sinus incision. This girl, 3½ years old, had bilateral purulent otitis media of two weeks' duration. No sulfonamide therapy had been given. She was found extremely septic on admission, with marked dehydration, anemia, enlargement of the liver and spleen, and blood culture positive for hemolytic streptococci. Both eardrums had sloughed away. There were no definite external signs of mastoiditis, but in association with cervical adenitis on the right side, there was purulent drainage through the external auditory canal with considerable hemorrhage. The x-rays indicated bilateral mastoid involvement, more on the right than the left. The Tobey-Ayer test was positive on the right. At operation, frank pus, without blood, was found in a white, compressible right lateral sinus, from which hemolytic streptococci were cultured.

improved treatment and has reduced the previous mortality rate of 28 to 35 per cent to approximately 10 per cent. Because of this, it should be added to the usual pre- and postoperative supportive measures, and, when properly administered and used in conjunction with proper operative measures, should (1) quickly abolish bacteremia, (2) prevent metastatic infection, (3) prevent postoperative spread of infection, (4) and help to reduce practically to zero mortality from hemolytic streptococcal lateral sinus phlebitis.

REFERENCES

1. Hartmann, A. F., and Cone, A. J.: South. M. J. **30**: 487, 1937.
2. Rüdinger: Quoted from Piersol's Human Anatomy, Philadelphia, 1930, J. B. Lippincott Co., p. 869.
3. Woodhall, B.: Arch. Surg. **33**: 297, 1936.
4. Woodhall, B., and Seeds, A.: Arch. Surg. **33**: 867, 1936.
5. Ersner, M. S., and Myers, D.: Laryngoscope **43**: 800, 1933.
6. Furstenberg, A.: Laryngoscope **50**: 950, 1940.
7. Furstenberg, A.: Tr. Am. Acad. Ophth. & Otolaryng., p. 424, 1937.
8. Hilding, A.: Arch. Otolaryng. **26**: 143, 1937.
9. Hoople, G. D.: Ann. Otol. Rhin. & Laryng. **45**: 1019, 1930.
10. Laff, H.: Arch. Otolaryng. **11**: 151, 1930.
11. Williams, H. L., Jr.: Arch. Otolaryng. **12**: 339, 1930.
12. Williams, H. L., and Hallberg, O.: Arch. Otolaryng. **33**: 78, 1941.

VITAMIN A ABSORPTION AND ITS RELATION TO INTESTINAL MOTILITY IN FIBROCYSTIC DISEASE OF THE PANCREAS

LEO J. FLAX, M.D., MARIAN BARNES,* M.D., AND
JOHN L. REICHERT, M.D., CHICAGO, ILL.

AS THE subject of pancreatic steatorrheas is becoming more clarified, and as fibrocystic disease of the pancreas has become more generally recognized, there have been an increasing number of patients diagnosed clinically. Only a very few of the reported patients have survived for any length of time after the diagnosis was made. The etiology of the disease is still uncertain, and no successful therapy has been devised, although some patients have been maintained for a time on a high protein and banana diet. All of the deaths occurring after the neonatal period have been the result of some respiratory infection.[1] This tendency to bronchopneumonia and bronchiectasis is very likely the result of changes in the bronchial epithelium due to vitamin A deficiency.[2] The inadequacy of vitamin A absorption has been shown to occur both in patients with the celiac syndrome and fibrocystic disease of the pancreas.[3-6]

The close association of gastrointestinal motility with carbohydrate absorption was demonstrated by May and McCreary[7] in celiac disease. This suggested that the absorption of vitamin A in fibrocystic disease of the pancreas might also be augmented when the gastrointestinal tone and peristalsis were increased. Such an attempt forms the basis of the therapy in our Case 1. The study was made doubly interesting by the birth of a second child in the same family, while the patient was still under treatment, who was also found to have fibrocystic disease of the pancreas and who is reported as Case 2.

CASE REPORTS

CASE 1.—B. S., a white girl, was born June 24, 1940. Labor and delivery were uncomplicated. The primiparous mother was 23 years old, 4 feet, 11 inches in height, and in good health. The mother was the fifth of the maternal grandmother's six pregnancies and is the only living child. The other five pregnancies resulted in premature births, the infants either being stillborn or living only a short time. The maternal grandmother is now 53 years old and is in good health. The maternal grandfather is 56 years of age, living and well. The patient's father is 27 years old and is 5 feet 3 inches in height. His mother died of diabetes; his father of a streptococcic infection. He has three living brothers and one sister. The latter has five living children, all of whom appear healthy.

Birth of the patient had been at full term; the infant was apparently healthy and weighed 5 pounds, 9 ounces. After several days she was placed on an evaporated

From The Children's Memorial Hospital.
*Otho S. A. Sprague Resident in Pathology.

milk and dextrimaltose formula because of an insufficiency of the mother's breast milk. At 10 days of age the child weighed 5 pounds, 8 ounces. When she failed to gain in the next three weeks, the feeding was changed to a biolac formula. She took cod-liver oil well. Because she refused orange juice, she was given 50 mg. of ascorbic acid daily. At 3½ months of age she was again placed on an evaporated milk formula. Later her feeding was changed to a mineral-modified whole cow's milk.

At 7 months of age she was sitting unsupported. At the age of 10 months she stood with support and walked with support at 15 months of age. She first talked at the age of 13 months. Her first tooth appeared at 8 months of age. Nutritionally she was consistently below the average. At 10 months of age she weighed 13 pounds; at 11 months of age, 14 pounds. From early infancy she vomited considerable amounts after each feeding.

The mother could not remember seeing normal stools. She described a typical stool as being large, in that she thought one stool was sufficient in bulk to account for the entire day's intake; but the baby had four to five such stools daily. They were dark in color, greasy, foul smelling, and either hard or spongy in consistency.

During the first ten months her physician repeatedly found evidence of acute bronchitis. In May, 1941, at the age of 11 months, she was coughing with sufficient severity and persistence to suggest a diagnosis of whooping cough. A series of injections of whooping cough vaccine was given. The cough became worse. She lost weight steadily. On three occasions she developed a prolapse of the rectum.

The patient was first seen by us in July, 1941. She was a small, undersized, poorly developed, and poorly nourished 13-month-old infant (Fig. 1). Her weight was 13 pounds, 8 ounces, and her height, 28 inches. She did not appear acutely ill but had a loose, deep, nonproductive cough. Her head was well shaped but seemed large in proportion to her body. The upper and lower incisors had erupted. The abdomen was rounded and protuberant, giving a distinct pot-bellied appearance. On palpation it had a doughy feel. The extremities were short and thin, and the musculature was weak and poorly developed. The buttocks were thin and flat. The remainder of the physical examination revealed nothing abnormal.

The blood contained 13.8 Gm. of hemoglobin. The total blood cholesterol was 114 mg. per cent. The Mantoux, 1:1,000, and the Kahn test were negative. Other laboratory studies were normal.

The x-ray of the chest was reported by Dr. W. E. Anspach: "There is soft tissue accentuation of the dependent bronchi along both heart borders—peribronchial inflammation. Otherwise the lung fields are clear. The heart is of normal contour and size."

The child was put on a diet of skimmed cow's milk and honey, mashed bananas, cottage cheese, strained vegetables, and meat. She was also given vipenta, 30 min. daily, and oleum percomorph, 10 drops, containing 41,000 I. U. of vitamin A, 4,700 I. U. of vitamin D, and an adequate amount of vitamins B and C. In addition she was given two 5 gr. capsules of enteric-coated pancreatic granules (panteric granules) daily. These capsules have been continued without interruption to date. In view of the history of early onset, failure to gain weight, chronic cough, x-ray findings in the lungs, and marked resistance to treatment, a diagnosis of fibrocystic disease of the pancreas was made.

The child was readmitted to The Children's Memorial Hospital in October, 1941, at the age of 16 months for further observation and study. She had gained to 14 pounds, 13 ounces, her appetite had improved, and generally she seemed more active. Her stools were still large and bulky, light brown or yellow in color, two to four in

number daily. Her cough was no better and a second x-ray of the chest, taken on Oct. 22, 1941, was reported by Dr. W. E. Anspach as follows: "The clouding noted below both hila stands out more clearly at this time (less exposure to x-ray). A lateral view shows the retrocardiac space slightly obliterated by the clouded area. The x-ray appearance is not unlike that we have seen in fibrocystic disease of the pancreas." (Fig. 3*A*.)

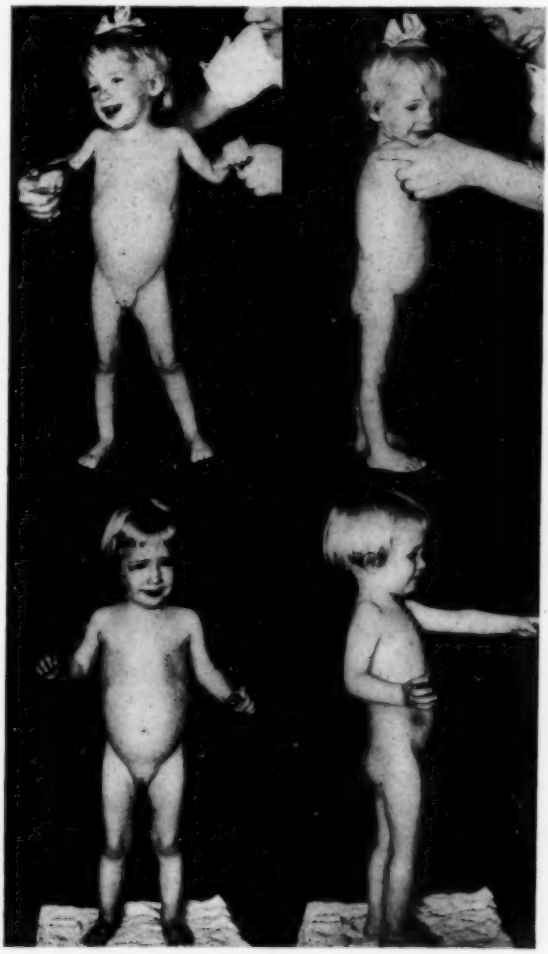


Fig. 1.

Fig. 2.

Fig. 1.—B. S. (Case 1) at the time of admission to the hospital at the age of 13 months.

Fig. 2.—B. S. (Case 1) at the age of 23 months.

A vitamin A absorption test was done, using the method of Chesney and McCoord.[8] The levels for vitamin A in the blood were determined by the Clausen and McCoord[9] modification of the Price and Carr method. A flat curve was obtained (Table I) with a maximum rise of 3 units.

The test was repeated following the hypodermic administration of prostigmine methylsulfate, 1:2000, 0.1 c.c. (0.05 mg.) t.i.d. on the day preceding and 0.15 c.c. at 8:00 A.M., 10:00 A.M., and 1:00 P.M. the day of the test. A more normal curve was obtained with a maximum rise of 60 units (Table I). A further test was done in which prostigmine bromide, 3.75 mg., was given orally t.i.d. the day before and day of the test. The six-hour level was 20.3 units, a rise of 14.8 units. The absorption test was repeated following the giving of one teaspoonful of fluidextract of cascara b.i.d. the day preceding and the day of the test, with a four-hour level of 30.6 units, a rise of 21.4 units above the fasting level. Complete vitamin A curves were not obtained because of the child's weak condition.

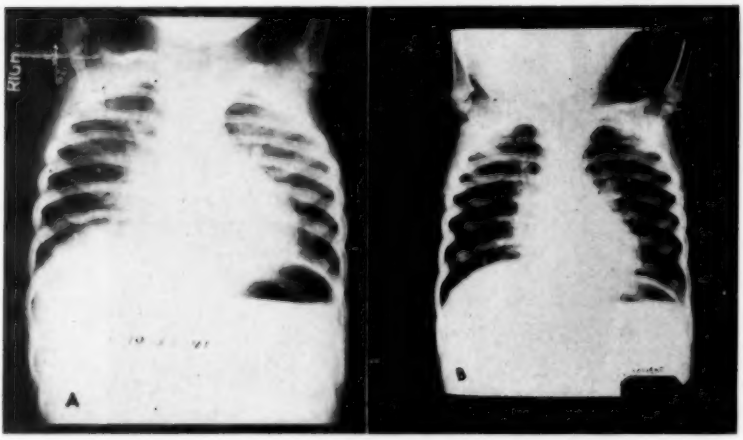


Fig. 3.—Chest roentgenograms of the patient B. S. (Case 1). *A* showing soft tissue accentuation of the dependent bronchi, and *B*, less clouding in the roentgenogram after five months of prostigmine and vitamin A therapy.

In every instance where a drug was used which might presumably cause an increase in intestinal tone and motility, the absorption of vitamin A from the gut seemed to be enhanced. Prostigmine methylsulfate subcutaneously, although the most promising, had the disadvantage of parenteral administration. The child was sent home, therefore, on a dosage of one-half teaspoonful of cascara b.i.d. She did well for the next two weeks, gaining about one pound. She had more normal stools, one to three in number daily. She then refused the cascara and the drug was discontinued. She developed an upper respiratory infection, and the cough became increasingly severe. She lost weight, and on Nov. 24, 1941, weighed 14 pounds, 14 ounces, but by Dec. 16, 1941, her weight was again up to 15 pounds, 9 ounces. Prostigmine bromide, 7.5 mg., t.i.d. was then started. During the next five months her weight gain was satisfactory, her appetite improved, and her cough diminished. She had one or two normal stools daily.

In May, 1942, the patient was readmitted to The Children's Memorial Hospital for recheck of the vitamin A absorption. Her appearance was markedly improved (Fig. 2). She weighed 18 pounds, 8 ounces, and was 31½ inches tall. Her extremities were muscular and sturdy, and she walked easily without support. She

TABLE I

VITAMIN A ABSORPTION TESTS

	PATIENT RECEIVING			
	PANTERIC GRANULES ONLY	PROSTIGMINE METHYL-SULFATE	PROSTIGMINE BROMIDE	CASCARA
Fasting	24*	12	5.5	8
4 Hr.	27	38		30.6
6 Hr.	15	72	20.3	
8 Hr.		63		
11 Hr.	11			
24 Hr.	20	18		

*Units of vitamin A in the blood.

had lost most of the prominence of her abdomen, and, in general, looked like a normal but undersized and slender 22½-month-old infant. Her strength and vigor were good; her appetite was excellent. The cough had improved, and the rectal prolapse was completely absent.

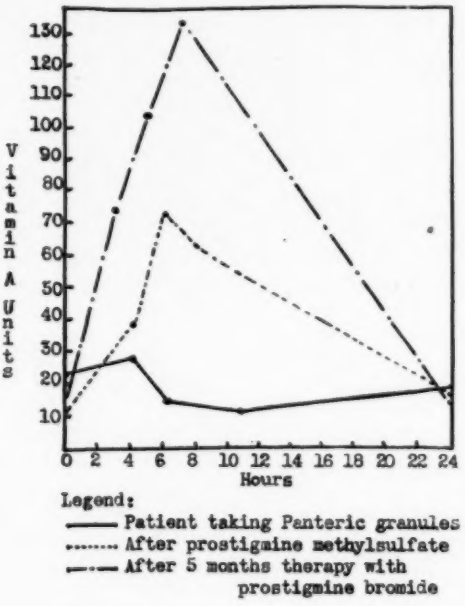


Fig. 4.—Vitamin A absorption curves.

The diet at this time consisted of one quart of skimmed cow's milk, cereal, two eggs daily, strained vegetables, ground or chipped beef, liver, salmon or chicken, cheeses, jello or puddings, stewed fruits, fruit juices, and graham crackers. In addition she ate about one banana with each meal, although her earlier enthusiasm for this fruit had definitely diminished. She was still taking 7.5 mg. of prostigmine bromide t.i.d. The dose of the pancreatic granules had been increased to 15 gr. t.i.d.; the vitamin A to 55,000 I. U. daily.

The x-ray of the chest showed some improvement of the lung with less clouding in the region of the right hilum (Fig. 3*B*). The total blood cholesterol at this time was 169 mg. per cent.

A vitamin A absorption test was done with the patient receiving her daily dose of prostigmine bromide and pancreatic granules. A curve was obtained with a maximum rise of 115 units to a level of 133 units at seven hours (Table II). This was well within the limits of vitamin A absorption in the normal child.

TABLE II

BLOOD SAMPLE	UNITS OF VITAMIN A
Fasting	18
3 Hr.	74
5 Hr.	104
7 Hr.	133
24 Hr.	17

A comparison of this curve with the previous vitamin A absorption curves is shown graphically in Fig. 4.

CASE 2.—On Jan. 12, 1942, when the patient, B. S., was 18 months old, a second child, C. S., was born to the parents. This was the second pregnancy and the baby was carried to term. The obstetrician who examined the infant girl a short time after birth stated that she appeared to be normal except that her abdomen seemed unduly large and tense. Five hours later a mass was found in the right side of the abdomen which felt like liver, but on later palpation seemed to have separated into several small masses. The abdomen soon became markedly distended and tympanitic. There were no bowel sounds. Meconium stains were seen on the diaper on several occasions. X-ray showed free air under the diaphragm. The diagnosis of intestinal perforation of unknown cause was made, and a laparotomy was performed by Dr. A. H. Montgomery when the baby was 41 hours old.

A congenital band was found crossing the ascending colon just above the cecum. This was not attached to the serosa of the bowel wall; a hemostat could be passed between it and the ascending colon. Proximal to this in the anterior surface of the cecum there was a large gaping hole that appeared to be a tear. This did not involve the appendix. The abdomen was filled with meconium and some fluid. The anomalous band was removed and the rupture in the cecum repaired. An iliocolostomy was made between the terminal ileum and the ascending colon. The infant died three hours after the operation was completed. She was 45½ hours old at death.

At autopsy an early peritonitis was found. *Bacillus coli*, a nonhemolytic streptococcus, and *Clostridium sporogenes* were isolated from the serosanguineous peritoneal fluid. The small gut was enormously distended and almost black in color. The odor was foul. The mesentery was stretched so that it contained innumerable small perforations, and its blood vessels were engorged. All the larger vessels were filled with recent, unorganized blood clot. From the third portion of the duodenum to the terminal ileum the gut was about four times as large in diameter as the colon. In spite of the distention, the gut wall was many times thicker and heavier than normal. In spite of the gangrenous color and odor, it could be handled freely and even bear tension. The lumen was filled with a semifluid, blood-stained material that appeared to be chiefly blood and sloughing mucosa. The iliocolostomy had retained all its sutures and its lumen was patent. Section of the ileum showed an extremely thick muscular coat. The mucosa was sloughing. The colon was small and thin walled, less than 1 cm. in diameter. Its lumen was empty except for a little mucus and small streaks of meconium. It was not unusually small for a new-

born infant. There was no atresia or stenosis of the entire length of the gastrointestinal tract. The anomalous band which was surgically removed appeared to be the only possible source of constriction of the lumen.

The uterus and vagina were large, the body of the uterus measuring 1 by 1.5 by 5 cm. The external os was large. There was a profuse mucous exudate in both the uterine cavity and the vagina. Sections showed large, distended mucous glands in place of the normal endometrium.

The lungs were atelectatic and edematous but without signs of infection. There were a few minor anomalies of the abdominal circulation but none of the heart or aorta.

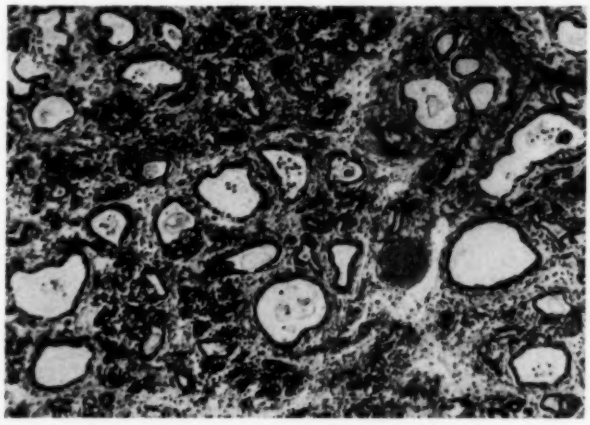


Fig. 5.—Photomicrograph of pancreas of patient C. S. (Case 2), who died at the age of 2 days.

The pancreas weighed 2 Gm. Except for hyperemia, the section grossly showed nothing unusual. The main pancreatic duct was traced for approximately 1 cm., well into the body of the organ. It opened into the duodenum through the ampulla. No obstruction was found. Microscopically, however, there was a diffuse cystic fibrosis affecting all parts of the pancreas equally (Fig. 5). Individual cysts were not extremely large, but every duct was distended to several times its normal size. The distention extended as far back as the acini, whose epithelium was flattened. Many of the dilated ducts contained only inspissated fluid. Some contained epithelial debris; a few contained leucocytes and necrotic debris. The marked interstitial fibrosis had destroyed much of the acinar tissue. There was a conspicuous sparing of the islet tissue.

No areas of squamous metaplasia were found in any of the epithelial surfaces of the body.

It is quite obvious that the pancreatic lesion contributed little or nothing to the infant's death. It is of interest chiefly because of the sibling's history and because it appears conclusive that the pancreatic abnormality may be present at birth.

DISCUSSION

Both Blackfan and May[3] and Andersen[1] have covered carefully and repeatedly the clinical findings and the histopathology of fibrocystic disease of the pancreas. Of the theories of the pathogenesis of the pan-

creatic lesion, Blackfan and Wolbach's[10] first hypothesis of abnormal secretions inspissating and causing obstruction of the ducts and acini seems the most plausible.

The familial nature of the disease has been stressed.[1, 11] The two cases here reported occurred in the same family. That the lesion is primarily congenital in nature is further borne out by the presence of the pancreatic changes at birth. Although Potter and Adair[12] do not describe fibrocystic disease under changes in the pancreas in their book on Fetal and Neonatal Death, five of the forty-nine cases listed by Andersen[1] were only 4 to 6 days old at the time of death. No evidence of pulmonary infection or of vitamin A deficiency was found at autopsy in either these five or our one case. In the other forty-four patients who died after the neonatal period and in the seven patients with the disease dying in the past two years at The Children's Memorial Hospital, the cause of death was a pulmonary infection. Twenty-three per cent and 28 per cent, respectively, of these patients had pathologic evidence of vitamin A deficiency. This agrees with the view first suggested by Parmalee[13] that there is present a poorly functioning pancreas which results in the inadequate absorption of the fat-soluble vitamins.

The inability to absorb vitamin A in and the closely allied nature of celiac disease make it likely that in addition to the pancreatic defect there may be some other agent associated with the etiology of fibrocystic disease of the pancreas. The factors involved in intestinal absorption are numerous. From the physical standpoint, absorption is closely dependent on the mechanical activity of the bowel which serves to bring into intimate contact the intestinal contents with the mucosa. Conversely, any impairment of this function such as would occur in intestinal hypotonia would interfere with efficient absorption.

X-ray study has demonstrated the hypotonicity, hypomotility, the delayed passage of the barium meal, and the so-called clumping characteristic or abnormal segmentation of the small bowel not only in celiac[7] and fibrocystic disease,[3] but in sprue[14] and vitamin B deficiency states[15] as well. Wade[16] reported the marked improvement in two patients with celiac disease in which cascara and posterior pituitary extract were used to increase intestinal motility. The association of gastrointestinal motility and tone with carbohydrate absorption was found by May and McCreary[7] to be a close one, as demonstrated by the marked rise in glucose absorption following the increased intestinal activity. Thus in both celiac disease and fibrocystic disease of the pancreas there is evidence of the functional derangement of the gastrointestinal tone and motility. Whether this results from a primary defect of the intrinsic nervous mechanism, or from a secondary one, due perhaps to a vitamin B deficiency, is not clear at the present time. In any case the inefficient absorption of vitamin A as well as of carbohydrate is apparently associated with the lack of tone and normal motility of the intestinal tract.

The successful use of prostigmine in restoring muscle tone in postoperative ileus[17] suggested its use in increasing the absorption of vitamin A in fibrocystic disease of the pancreas by an improvement of the intestinal tone. An enhanced absorption, it was believed, should not only improve nutrition but could be expected to obviate the vitamin A deficiency and so prevent the pulmonary infection which was usually the cause of death.

The parenteral administration of prostigmine methylsulfate to the patient gave an almost immediate rise in the blood level of vitamin A. The trial use of the bromide salt orally also seemed justified, and the clinical response was gratifying. A check of the vitamin A absorption after a period of five months, during which time 7.5 mg. of prostigmine bromide was given t.i.d., showed a normal curve (Fig. 4). The child tolerated the drug very well and was without any toxic symptoms or ill effects. The diminution in the cough and the lessened peribronchial infiltration in the lungs as shown by x-ray (Fig. 3*B*) are the objective evidence of the improvement in the patient's ability to absorb vitamin A. The rise in the total blood cholesterol level from 114 mg. per cent to 169 mg. per cent would suggest an increased lipid absorption as well. Since carotene, the precursor of vitamin A, is absorbed from an isolated intestinal loop more readily in the presence of bile and pancreatic lipase,[18] it seemed logical to substitute whole pancreas in the form of enteric-coated pancreatic granules (panteric granules) as an additional measure.

The therapeutic regimen, in brief, consisted of a high caloric, high protein, moderately low fat, low starch diet; pancreatic granules, 1 to 5 Gm. daily; vitamin A, 50,000 I. U. daily in divided doses; adequate amounts of vitamins B, C, and D; and prostigmine bromide, 3.75 to 7.5 mg. t.i.d.

SUMMARY

Studies on the vitamin A absorption in a patient with fibrocystic disease of the pancreas show an apparent close relationship with gastrointestinal tone and motility.

Prostigmine is suggested as an addition to the therapy of the disease, as a means of increasing the absorption of vitamin A.

The congenital nature of the pancreatic lesion is suggested by the presence of the fibrocystic changes in the pancreas of the second sibling, whose death occurred forty-five and a half hours after birth.

The vitamin A determinations and other laboratory studies were done by Miss Grace Lawrence.

REFERENCES

1. Andersen, D. H.: Am. J. Dis. Child. **56**: 375, 1938.
2. Andersen, D. H.: J. PEDIAT. **15**: 769, 1939.
3. Blackfan, K. D., and May, C. D.: J. PEDIAT. **13**: 623, 1938.
4. May, C. D., and McCreary, J. F.: J. PEDIAT. **18**: 200, 1941.
5. Breese, B. B., and McCoord, A. B.: J. PEDIAT. **15**: 183, 1939.

6. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H.: Am. J. Dis. Child. **59**: 1167, 1940.
7. May, C. D., and McCreary, J. F.: J. PEDIAT. **17**: 143, 1940.
8. Chesney, J., and McCoord, A. B.: Proc. Soc. Exper. Biol. & Med. **31**: 887, 1934.
9. Clausen, S. W., and McCoord, A. B.: J. PEDIAT. **13**: 635, 1938.
10. Blackfan, K. D., and Wolbach, B. S.: J. PEDIAT. **3**: 679, 1933.
11. Rauch, S., Litvak, A. M., and Steiner, M.: J. PEDIAT. **14**: 462, 1939.
12. Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death, Chicago, 1940, The University of Chicago Press.
13. Parmalee, A. H.: Am. J. Dis. Child. **50**: 1418, 1935.
14. Snell, A. M., and Camp, J. D.: Arch. Int. Med. **53**: 615, 1934.
15. Lepore, M. J., and Golden, R.: J. A. M. A. **117**: 918, 1941.
16. Wade, A. E.: J. PEDIAT. **8**: 563, 1936.
17. Marden, P. A., and Williamson, E. G.: Surg., Gynec. & Obst. **69**: 61, 1939.
18. Irvin, J. L., Kopala, J., and Johnston, C. G.: Am. J. Physiol. **132**: 202, 1941.

OBESITY IN CHILDREN

I. P. Bronstein, M.D., L. J. Halpern, M.D., and
A. W. Brown, Ph.D., Chicago, Ill.

OBESITY in childhood is the most common so-called endocrinopathy encountered in pediatric practice. The prevalent assumption that obesity is usually an expression of some underlying endocrine dysfunction has led to the indiscriminate, if not harmful, administration of various endocrine products in the hope of curing this disorder. Recent excellent work[1] has, however, emphasized the fallacy of such an assumption, and the suggestion has also been made that the term Fröhlich's syndrome, to designate markedly overweight children, be deleted from the nomenclature.[2]

For a number of years we have been investigating this problem. During this time, several hundred obese children of variable ages with a tentative diagnosis of Fröhlich's syndrome have been referred to us for study. We have attempted to find evidence, clinical, laboratory, or both, which might substantiate an underlying endocrine causation for their obesity and to study, at the same time, the effect of diet, various glandular products, and special drugs on this condition.

PROCEDURE OF STUDY

Our investigation comprised a complete initial history and physical and laboratory examinations of each child on admission and at regular intervals thereafter until this last visit. The history included information on each child's type of delivery, birth weight, and condition at birth, the onset of obesity together with any suspected relationship to some illness, accident, or surgical measure, the type and quantity of food as well as the amount of fluids consumed daily, whether the appetite was voracious, moderate, or poor, whether a child was lazy or active, and the incidence of obesity or any endocrine disorder in other members of the family as well as their inclination toward short or tall stature.

The physical examination included general and regional observations with special emphasis being given to the amount and per cent overweight as well as the height attainment of each child compared with reliable standards, the distribution of fat, shape of the hands, sexual development, and the status of the ocular fundi and visual fields.

The laboratory examination included a study of each child's metabolic activity as judged by repeated basal metabolic determinations, using several standards for computation, and by the cholesterol content of the

From the Department of Pediatrics (Endocrine Clinic) and the Institute for Juvenile Research, University of Illinois, College of Medicine, and the Research and Educational Hospital.

blood. The difficulties encountered in applying normal standards to subjects of abnormal body proportions were recently emphasized by one of us.[3] Logan and associates[4] feel that the basal metabolism of the fat individual is the resultant of the two following factors: (1) a faster metabolism of the nonfatty tissue and (2) the small increment from the cells of the adipose tissue. Sugar tolerance studies by the Exton-Rose method,* the recording of the blood pressure with the use of an appropriate cuff,[5] the study of osseous growth, as judged by roentgenograms of the wrists and knees, and the attempt to detect any irregularity or abnormality in the size and shape of the pituitary gland by means of roentgenograms of the skull were carried out routinely. In indicated cases, other examinations, such as visualization of the genitourinary tract, were also done. In addition, a number of these children underwent a cephalometric[6] and psychologic appraisal.[7]

MATERIAL

Although several hundred children suspected of presenting adiposogenital dystrophia were referred to us, eighty of these were accepted at random for a comprehensive examination. Of this number, forty-six cooperated sufficiently well in returning at stated intervals for repeated physical and laboratory check-ups so that only they are included in this report. While all of these forty-six children were referred to us because of their obvious obesity, this was not always the primary complaint which provoked their seeking medical aid. In nine instances, undersized genitals, and in nine others, undescended testicles were either the primary or associated complaints. Other primary or associated complaints included three instances of "not growing fast enough," two of periodic headaches accompanied in one by nausea, and one each of "growing too fast," irregular menstruation, epilepsy, epileptic-equivalent, and eczema. Warkany and co-workers,[4] in his series of 140 obese boys and girls, found that about one-half of these children had associated nonendocrine conditions, such as abnormalities of the nervous and skeletal systems and enuresis.

The forty-six children under observation consisted of twenty-eight males and eighteen females. There was a family history of obesity in seventeen children, diabetes in four, goiter in four, and asthma in one. Four of the forty-six children were Jewish, five Italians, and the balance were of other various combined extractions too complex to categorize. The fact that Jewish children indulge in rich and sweet foods and Italians in starchy foods like spaghetti and macaroni may have some bearing on their proportional preponderance in a group of obese children.

*Sugar tolerance tests were included since some authors indicate these may be of some value in indicating pituitary dysfunction. The results of these tests will be reported separately and compared with determinations in other conditions in an attempt to assay the part that this test can contribute to an understanding of the various conditions studied.

The average age of the entire forty-six children on admission was 10 years and 11 months. The twenty-eight males averaged 11 years, 2 months; the eighteen females, 10 years, 8 months. The youngest child was 4 years, 10 months, and the oldest, 15 years. The average weight of the entire group on admission was 134¾ pounds, or 57 per cent overweight. The twenty-eight males were 55 per cent overweight compared to 59 per cent in the eighteen females. Eight of the forty-six children were more than 80 per cent overweight, three of which were 104 per cent, 108 per cent, and 128 per cent overweight, respectively. The average height attainment of the entire group on admission was fifty-seven inches compared to sixty inches, which is the average tall limit, and forty-seven inches, which is the average short limit for children of similar average ages.

PROGRESS OF INVESTIGATION

Tables I and II represent the individual record of each child and a composite one of all the forty-six children, emphasis being placed on the sex, age, and per cent overweight on admission compared to the last visit, duration of observation, and the type of treatment administered. Detailed data of physical and laboratory findings in each instance are omitted because of their great length. Whereas this study is a summary of our material, we are reporting in another paper[8] two individual cases, one female child of normal intelligence and the other mentally deficient, which represent in detail the progressive changes in the diagnosis and treatment of obesity over a considerable period of years.

The average duration of observation for the entire forty-six children was two years and one month, although one child was observed for over six years, two for over five years, four for over four years, four for over three years, and three for over two years, thus making a total of fourteen children, or one-third of the entire group, that were observed for a period ranging between two and six years, while the balance were observed for a period ranging between six months and two years.

Throughout this study and at its conclusion, we were unable to find evidence of a single case of endocrine dysfunction in any of the forty-six obese children. However, it cannot be overemphasized that obese children should be thoroughly studied in order to detect the occasional instance where a pathologic disturbance may underlie the adiposity. Apropos of this are three children who were referred to us with a tentative diagnosis of Fröhlich's syndrome but whom we were unable to observe completely because of variable circumstances:

1. A girl aged 14 years revealed in routine roentgenograms of the skull diastases of the sutures and erosion of the sellar walls. The ocular examination showed bilateral choking of the discs and constriction of the visual fields. She died suddenly at another institution following ventriculographic examination. The pathologic studies at autopsy revealed,

TABLE I

INDIVIDUAL RECORD

CASE NO.	NAME	SEX	ADMISSION AGE		PER CENT OVERWEIGHT		DURATION OF OBSERVATION		TREATMENT
			YR.	MO.	ADMISSION	LAST VISIT	YR.	MO.	
1	A. B.	F	11		50	58	1	8	D. and T.
2	H. B.	M	7	6	67	54	2	9	D.
3	G. B.	M	14		84	82		1.5	D. and T.
4	L. D.	M	12	5	76	78	4		D.
5	J. C.	M	9		39	22	3	11	D. and CG.
6	I. C.	F	11	10	89	71		8	D.
7	L. C.	F	10	9	61	66	4	5	D.
8	W. C.	M	13	6	66	73	1		D.
9	P. A.	M	10		84	67	2	3	D.
10	M. B.	M	8		18	31	2	2	D. and CG.
11	A. D.	F	11	5	71	59		4	D.
12	C. J.	M	9	11	34	1	6	3	D. and CG.
13	D. H.	F	12		48	32		8	D.
14	B. H.	F	8		56	13	4		D. and T.
15	D. G.	M	8		53	30	1	2	D.
16	E. E.	F	13		55	58	3		D.
17	D. G.	F	9	9	54	85	5	7	D., T., CG., AP., and Dr.
18	L. L.	M	14	6	49	37		10	D., T., and CG.
19	R. M.	M	11	6	27	20	1	11	D. and T.
20	R. M.	F	10	6	45	37	1	1	D.
21	M. N.	F	15		39	24	1	2	D.
22	M. N.	F	8	6	84	72		9	D.
23	F. P.	M	12	2	79	53	1	11	D.
24	D. P.	F	12	10	26	8	4		D.
25	G. S.	M	11	7	45	42	1	9	D., T., and CG.
26	B. S.	M	11	6	33	26	1	10	D. and CG.
27	G. R.	M	11		50	41	1	2	D. and CG.
28	J. S.	M	14	4	38	38	1	2	D.
29	H. S.	M	9		62	47	1	1	D.
30	L. T.	M	10	5	44	24	2	3	D., T., and CG.
31	T. V.	M	11	4	75	60		10	D.
32	B. V.	F	7	2	27	48	3	1	D., T., CG., AP., and Dr.
33	A. Z.	F	9	3	105	72	4	4	D., T., CG., and AP.
34	E. B.	M	12	5	60	61	2		D. and CG.
35	H. P.	M	12	3	82	80		6	D.
36	L. P.	F	11	4	46	30		9	D.
37	L. S.	F	6	2	62	71	5	6	D., T., CG., and AP.
38	J. K.	M	13	3	71	69		2	D. and CG.
39	D. H.	M	13	4	22	18		11	D. and CG.
40	J. B.	M	11		46	27	3		D., T., and CG.
41	R. F.	F	4	10	104	90		6	D.
42	A. P.	F	8		46	37	2	6	D. and T.
43	L. M.	M	9	1	27	45	2	6	D.
44	G. M.	M	8	6	73	66		3	D.
45	D. Mc.	M	13	5	128	153	1	7	D. and Dr.
46	Th. M.	M	13	1	59	70		2	D. and CG.

D. = Diet.
T. = Thyroid.
CG. = Chorionic gonadotropin.
AP. = Anterior pituitary.
Dr. = (Benzedrine) amphetamine sulfate.

TABLE II

COMPOSITE RECORD

(AVERAGE)

SEX	NUMBER OF CASES	ADMISSION AGE		PER CENT OVERWEIGHT		DURATION OF OBSERVATION (MO.)
		YR.	MO.	ADMISSION	LAST VISIT	
Males	28	11	2	56.5	50.5	20.3
Females	18	10	8	59.3	51.8	29.3

in addition to other features, glial overgrowth extending into the fourth ventricle obstructing the foramina of Luschka and Magendie.

2. A boy aged 13 years (Fig. 1) exhibited, in addition to mamillary and abdominal obesity, an enormous accumulation of fat around the face and the upper part of the trunk. His penis and testes were small, some pubic hair was present, and there was some down on his face. On numerous occasions after resting, the blood pressure readings were 150 mm. mercury systolic and 118 mm. diastolic. The urograms were definitely abnormal, but unfortunately, due to lack of cooperation, further study, such as retropyelo ureterography and perirenal air insufflation, were impossible. Quite recently, Marks and his collaborators[9] reviewed the literature and reported a case of their own in which adiposity and elevation of blood pressure were the outstanding symptoms in a child with an adrenocortical tumor. This striking monstrous obesity of the so-called buffalo type plus an elevated blood pressure is said to be characteristic for obesity of adrenal origin.

3. A boy aged 4 years with a left hemiplegia (Fig. 2) exhibited marked obesity. There was a history of a very difficult delivery with high forceps, probably resulting in an intracranial hemorrhage with subsequent involvement of the diencephalon, which might be suspected of underlying his obesity.

In view of the negative findings obtained in our forty-six children, our management consisted of limiting the daily diet to between 1,000 and 1,500 calories, restricting the fluid intake, and assuring an adequate daily consumption of the essential vitamins. In a number of instances, glandular extracts by mouth or by injection had been administered in variable amounts before they were referred to us for study. Obviously, their referral to us after such treatment attested to the ineffectiveness of such therapeutic procedures. Even though our treatment was at first dietary only, associated complaints like undescended testicles and small genitals dictated that this be complemented later by the customary forms of endocrine therapy. Too, when adherence to the limited diet was poor, or repeated basal metabolism tests were appreciably low, thyroid extract by mouth was administered in addition to the prescribed diet. As a result, only twenty-five (54 per cent) of our forty-six children received as their sole treatment a restricted diet.

The average weight of the entire forty-six children on the last visit was 149 pounds, or 52.7 per cent, overweight compared to 134¾ pounds, or 57 per cent, overweight on admission. The twenty-nine males who were 55 per cent overweight on admission were 50.4 per cent overweight on the last visit, while the eighteen females were 55.1 per cent overweight on the last visit compared to 59 per cent on admission. The

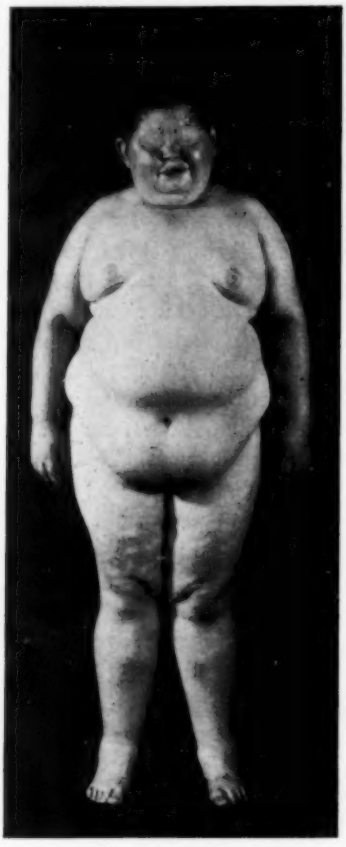


Fig. 1.

twenty-five children who were treated by diet only and who averaged 64 per cent overweight on admission were 55 per cent overweight on the last visit. It is apparent that the average reduction of weight in the group as a whole at the end of our period of observation was negligible regardless of the type of treatment used. Better results were obtained in the group treated solely by diet but, with them too, the reduction of weight was the greatest when they cooperated in adhering to the limited diet. This is conspicuous in Cases 15, 21, 44, and 46 in

Table I. It is interesting to note that six patients gained weight on dietary treatment, but there again, cooperation was poor. On the other hand, the patient in Case 24 was uncooperative but lost weight anyhow.

Weight reduction was equally negligible when glandular extracts complemented the dietary treatment. For example, the patient in Case 19 received 290 gr. of thyroid extract by mouth during the latter twelve months of the twenty-three months of observation with a weight reduction of only 7 per cent. In Case 25 the patient had 350 gr. irregularly

Fig. 2.

during three months without effect on his weight. The patient in Case 33 had thyroid extract, posterior pituitary parenterally, and whole pituitary by mouth for three years prior to admission with no effect on his weight, and he had 114 gr. of thyroid under our observation with similar results. In Case 37 the patient had 2,000 gr. of thyroid in six years prior to our study, lost but little weight during that time, and gained rapidly before admission when thyroid was discontinued. The patient in Case 42 had thyroid for eight months after admission but gained weight. The patients in Cases 32 and 37, both retarded mentally,

had the whole gamut of treatment with but little success. In addition to food restrictions and thyroid extract, the patient in Case 32 received parenterally 4,000 R.U. of chorionic gonadotropic hormone and 75 c.c. of whole anterior pituitary extract. In Case 37 the patient was given 9,200 R.U. of gonadotropic hormone from pregnant urine.

Failure to obtain an appreciable and consistent reduction in weight by all other methods of treatment prompted us to use amphetamine sulfate (benzedrine) in a small number of our patients. This resulted in a loss of appetite with a decrease of food intake and a consequent initial success in weight reduction. However, this was usually short-lived. The patient in Case 17, for example, received 10 to 30 mg. of amphetamine sulfate daily until several hundred milligrams had been taken without any ill effect and without any effect on her obesity. In Case 32 the patient received 2,250 mg. of this drug following dietary and glandular treatment, but the tablets were discontinued eighteen months before her last visit because of their ineffectiveness. In Case 44 the patient had 450 mg. in three weeks and another 210 mg. during the following month without a decrease in the obesity. It was our impression that this drug given even in large quantities had little untoward effect on our patients.

In addition to observing the progress of obesity in the forty-six children, it is also interesting to note their progress of sexual development during this period. Of the nine males who exhibited undersized genitals on admission, six of them revealed normal development of these organs on the last visit, while only three were still undersized. Of the nine instances of cryptorchidism on admission, in three, in whom the condition was bilateral (not migratory), descent had occurred when last seen, while in the five with unilateral cryptorchidism, descent had not taken place when last seen, even with recognized adequate therapy. In the remaining boy who had presumably bilateral abdominal cryptorchidism which 100,000 R.U. of gonadotropic material failed to affect, bilateral orchidopexy was performed.

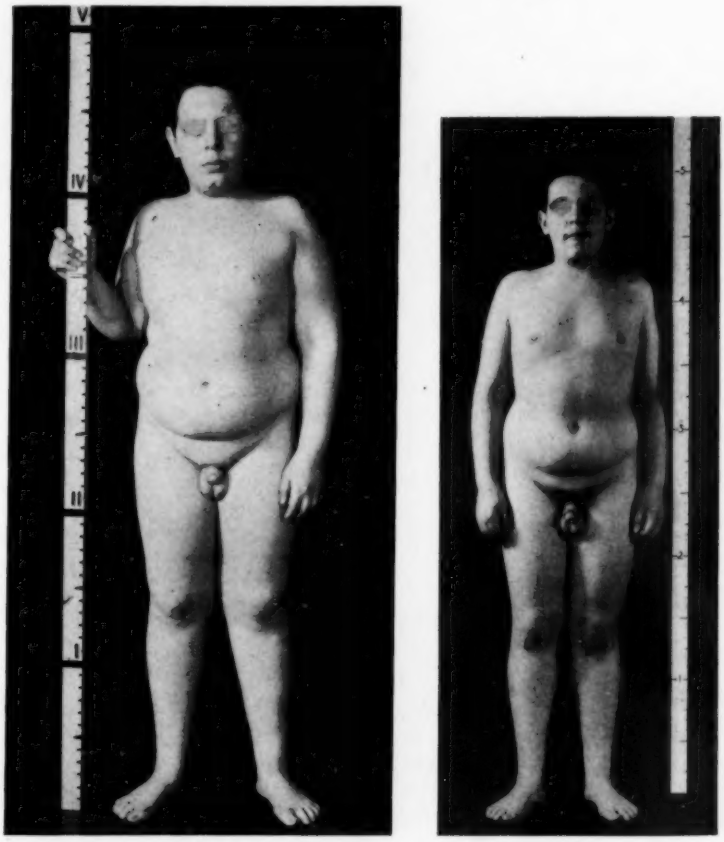
Of the twenty-eight males, eight had pubic hair and two had both pubic and axillary hair on admission. At the last visit eleven had pubic hair and five both pubic and axillary hair. Of the eighteen females, six had pubic hair and three had both pubic and axillary hair on admission. At the last visit eleven had both pubic and axillary hair, while three who revealed no hair on admission had pubic hair. Of the total forty-six children, twenty-nine had either pubic or both pubic and axillary hair on the last visit as compared to nineteen on admission.

Of the 18 females, on admission only one had begun to menstruate and her periods were irregular. At the last visit there were six who were menstruating regularly and another who had begun to menstruate irregularly. The girls in our series matured a little sooner than did the

boys. In the female children it is much more difficult, especially before secondary sexual characteristics appear, to correctly designate hypogenitalism.

DISCUSSION AND CONCLUSIONS

Of a large group of children referred to us whose conditions were tentatively diagnosed as Fröhlich's syndrome, forty-six children ranging from 4 to 15 years, with an average age of 10 years, 11 months, comprise this report. The average per cent of overweight was 57, 8 of the patients being more than 80 per cent overweight.

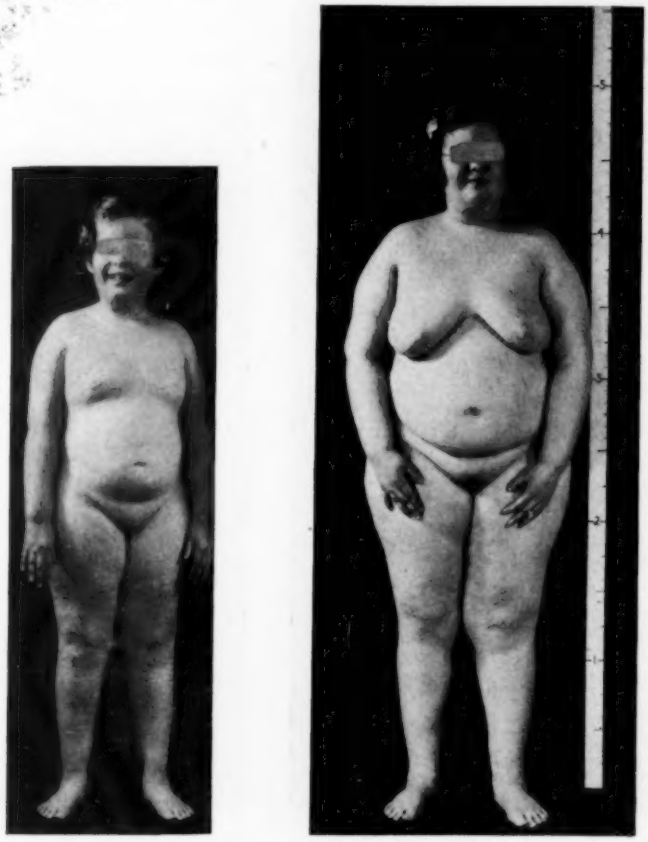


A. *B.*

Fig. 3 (Case 18).—*A*, L. L. at age of 14½ years. Evidence of delayed puberty (?). *B*, L. L. one year later. Spontaneous correction without therapy.

History and physical and laboratory examinations of each child on admission and at regular intervals thereafter until the last visit, over an observation period ranging from six months to six years, with an average of two years, one month, were conducted to establish any evi-

dence of glandular dysfunction as a possible basis for the obesity. None was found. The data on the boys as well as on the girls pertinent to sexual development gave little evidence of involvement of either the pituitary or thyroid. Cephalometric roentgenographic analysis[6] of the craniofacial skeleton showed that in general the development in this group of children is normal and even slightly in advance of normal controls. Tooth eruption was accelerated, whereas in hypopituitarism[10] and hypothyroidism[11] it is retarded. Hypercholesteremia, which may exist with thyroid deficiency,[12] was not found in our obese children nor in Bruch's[13] series.



A. *B.*

Fig. 4 (Case 37).—*A*, L. S. at age of 8 years. Mental retardation present. *B*, L. S. at age of 13½ years. Condition unchanged; had all forms of therapy.

A psychologic study[7] to determine whether the milieu of a group of obese children was of a characteristic type predisposing them to overeating, in which many of them indulge, has recently been reported by

us. The excessive appetite is certainly pathologic in many instances, and whether the responsibility resides in the hypothalamus is difficult to ascertain.

Ritter,[14] in an histologic study of the hypothalamus and the adjoining regions in four types of obesity, including the so-called constitutional type, found the morphologic changes without significance, although the hypophysis showed severe basophilism in all four. The basophilism was not regarded as the cause of the obesity but represented rather a compensatory process elicited by the disturbance in the equilibrium of the endocrine organs involved in fat metabolism.

Farber,[4] in discussing the knowledge of the pathologic-physiologic background of adiposity, indicates its association with vascular lesions involving the diencephalon. In summary he states that with the exception of severe adiposity associated with certain examples of adrenal cortex tumor, the pathologic lesion underlying adiposity and adiposogenital dystrophy is to be found for the most part in the brain and may be associated particularly with involvement of the hypothalamus.

The treatment for obesity in our series consisted mainly of restricting the diet and fluid intake, exercise, and adding ample vitamins. When the child adhered to this regime, a moderate loss of weight followed in most instances, but the majority refused to cooperate from the beginning or after a relatively brief interval.

Oral administration of thyroid extract in large daily doses over fairly long intervals did not cause loss of weight in most instances. Chorionic gonadotropins or whole anterior pituitary extract given parenterally in even large doses failed to influence the weight. Amphetamine sulfate, while immediately effective in causing a reduction of weight by depressing the appetite, lost its effect soon after the drug was stopped, and in some instances even while the drug was being taken.

From the foregoing it is apparent that no appreciable loss of weight was effected in our series of patients regardless of the type of treatment used. However, we wish to emphasize that in our experience over a long period of observation, obesity in mentally adequate children tends to correct itself at or about puberty, at which time they become cognizant of their obesity as a handicap and are then willing to cooperate satisfactorily in a dietary regime (Figs. 3*A* and 3*B*, Case 18) (Figs. 4*A* and 4*B*, Case 37).

REFERENCES

1. Bruch, H.: Am. J. Dis. Child. **58**: 457, 1939; Am. J. Dis. Child. **59**: 741, 1940; Am. J. Dis. Child. **60**: 1082, 1940.
2. Bruch, H.: Am. J. Dis. Child. **58**: 1282, 1939.
3. Poncher, H. G., Bronstein, I. P., Wade, H. W., and Ricewasser, J. C.: Am. J. Dis. Child. **63**: 270, 1942.
4. Logan, M. L., Farber, S., and Warkany, J.: J. PEDIAT. **19**: 855, 1941.
5. Day, R.: J. PEDIAT. **14**: 148, 1939.
Robinson, M., Hamilton, W. F., Woodbury, R. A., and Volpitts, P. P.: Am. J. Dis. Child. **58**: 102, 1939.

6. Bronstein, I. P., and Massler, M.: Cephalometric Appraisal of Obesity in Childhood. Unpublished data.
7. Bronstein, I. P., Wexler, S., Brown, A. W., and Halpern, L. J.: Am. J. Dis. Child. **63**: 238, 1942.
8. Halpern, L. J., and Bronstein, I. P.: Unpublished data.
9. Marks, T. M., Thomas, J. M., and Warkany, J.: Am. J. Dis. Child. **60**: 923, 1940.
10. Massler, M., and Bronstein, I. P.: Cephalometric Appraisal in Dwarfism. Unpublished data.
11. Engel, M. B., Bronstein, I. P., Brodie, A. G., and Wesoke, P.: Am. J. Dis. Child. **61**: 1193, 1941.
12. Bronstein, I. P.: J. A. M. A. **100**: 1661, 1933.
13. Bruch, H.: Am. J. Dis. Child. **58**: 1001, 1939.
14. Ritter, W.: Frankfurt. Ztschr. f. Path. **52**: 149, 1938.

ENTEROBIASIS IN CHILDREN

Incidence, Symptomatology, and Diagnosis, With a Simplified Scotch Cellulose Tape Technique

Alvin H. Jacobs, M.D.
San Francisco, Calif.

RECENT studies indicate that *Enterobius vermicularis* infestation is a common and frequently overlooked disorder of childhood. The present paper is a study of the incidence and symptomatology of infestation with pinworms, as well as a presentation of a simplified, efficient method for diagnosis.

The pinworm (*Oxyuris vermicularis* or *E. vermicularis*) is a member of the Nemathelminthes, or round worms. This worm is quite universal in distribution, being found in tropical and temperate regions alike. It is most common in members of the same family and among children in institutions. The adult worms live in the lower bowel and appendix with their heads attached to the mucosa. The male is 2 to 5 mm. long, while the female is 8 to 13 mm. long. As the female becomes distended with eggs, she releases herself from the mucosa, crawls out at night and deposits eggs in the perineal folds and in the vagina. Eggs are not commonly laid within the bowel. The eggs are then transmitted by finger to the mouth of the same host or that of another. There is no intermediate animal host. Bed linen contamination is a common source for others in the family.[1]

METHODS OF DIAGNOSIS

NIH Method.*—In 1937 Hall[2] described a device for the diagnosis of enterobius infestation which made it possible for the first time to diagnose a large proportion of the infested individuals. Hall pointed out that since the eggs of this worm are not deposited within the intestinal tract but rather in the folds of skin about the anus and genitals, it is not likely that the eggs can be found in the stools in more than a small proportion of the infested patients. He experimented with various methods of swabbing and scraping the perianal skin for the eggs and finally devised the NIH swab, which consists of a small square of cellophane wrapped about the rounded end of a glass rod. The pinworm eggs stick to the cellophane when the perianal region is stroked with the swab. The cellophane is then removed and placed in a drop of water on a slide and examined directly for ova under the microscope.

Scotch Cellulose Tape Method.—If the NIH swab is used routinely on any large number of patients, it requires a considerable portion of

From the Department of Pediatrics, Stanford University School of Medicine.
*National Institute of Health.

a technician's time preparing the swabs and cleaning the used glass rods carefully in order to remove all of the ova remaining from the previous examination.[3] In order to eliminate this objection and at the same time to supply an adhesive surface to which the ova are more likely to adhere, I decided to use Scotch cellulose tape, an inexpensive, transparent, adhesive tape. After completing this study I found that the use of Scotch cellulose tape for the diagnosis of pinworms had previously been described by Graham,[4] although he did not report any results with its use. The only materials needed are a roll of tape, wooden tongue blades, and glass microscope slides. A piece of Scotch tape about the length of the slide is folded over one end of a tongue blade with the nonadhesive surface of the tape against the tongue blade. The ends of the tape can be held in place by the examiner's fingers. Using this as an applicator and applying it to the perianal folds, the pinworm eggs are picked up by the sticky surface of the tape, which is then removed from the tongue blade and spread out, adhesive surface down, on the slide and examined directly under the low power of the microscope without the use of a cover slip. If desired, the slides can be placed in a slide box and examined at the physician's convenience. These slides may be kept for many days without any change in the appearance of the ova. In most instances, if eggs are present they are in large enough numbers so that a rapid survey of the slide under low power reveals many of them.

It is wise in each positive case to examine at least one of the eggs under high power, which enables one to see the embryo and to observe its movements within the egg under the influence of the heat of the microscope lamp (Fig. 1).

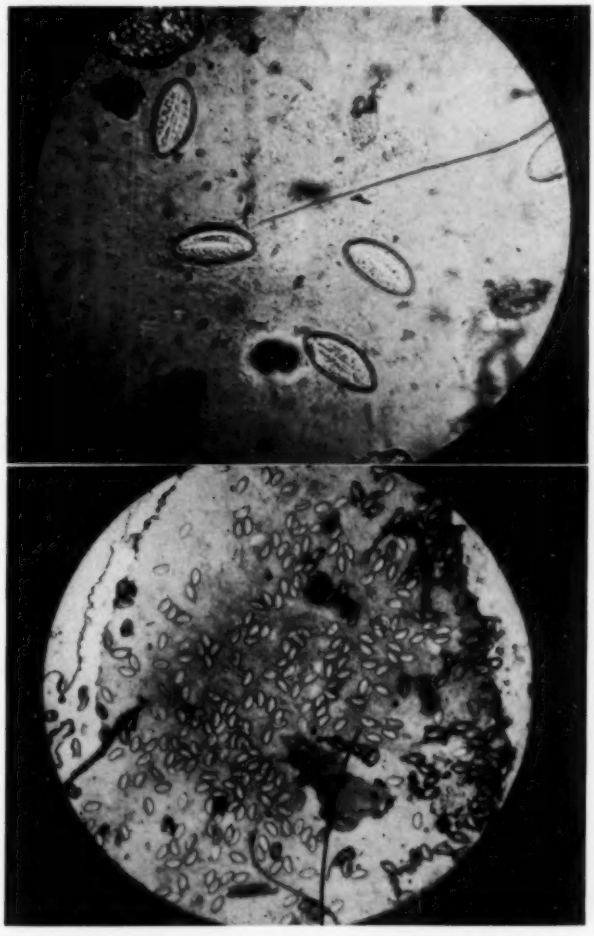
Reardon[5] studied plain cellophane microscopically for artefacts which might simulate enterobius ova but found none that would be misleading. I have studied many samples of Scotch tape under the microscope and have found no artefacts that might be confused with typical ova. Occasionally an air bubble will assume the shape of a pinworm egg, but high-power examination will reveal the absence of any embryo.

The Scotch tape technique has the advantage of simplicity and efficiency. The materials needed for the test are already present in most physicians' offices, and the examination takes but a few moments. Hall's statement about the original NIH swab applies equally well to this method: "It picks up eggs dependably; delivers the entire take to a microscope slide dependably and with little manipulation of any sort and none for separating eggs from the contact part of the swab; it is easy to transport without loss of eggs collected and with safety to those handling it; and causes the patient no discomfort in its use."[2]

INCIDENCE

The very high incidence of enterobius infestation was not appreciated until the advent of the NIH swab made possible more accurate diagnosis.

At the present time it is still not generally realized that enterobius infestation is the commonest of all helminthiases. The first extensive epidemiologic studies of oxyuriasis using the NIH swab were reported by Cram and his associates of the National Institute of Health. They first reported in 1937[6] a series of 1,272 persons examined in Washington, D. C. The individuals were of all ages and walks of life, seen both



B.

A.

Fig. 1.—Photomicrographs of the ova of *Enterobius vermicularis* as seen on Scotch cellulose tape. *A*, ×100; *B*, ×430.

in clinics and in private practice. They found 35.4 per cent to be infested. Ninety-four per cent of the positive cases were detected on either the first or second NIH examination, but as many as six swabs were necessary to diagnose one case. The first examination detected only one-half of the cases found to be positive after four examinations. It was also found in this study that only one out of ten of the positives

was detected by stool examination. They concluded that "oxyuriasis is by far the commonest and most neglected of all human helminthiases."

In a later expansion of the above study, Cram and his associates[7] examined 2,097 persons from the general population, from hospital clinics, nursery schools, and private practice. Of these, 41 per cent were positive. The positive cases when broken down into age groups were: preschool age, 35 per cent; school age, 51 per cent; and adults, 22 per cent. They found the problem to be unrelated to population groups as regards sex, race, age, social-economic status, or location of residence.

Weller and Sorenson[8] examined an unselected series of 505 white patients between the ages of 2 and 12 years in Boston. Of these, 118 were seen on the ward of a children's service, while 387 were seen in the outpatient department. The NIH swab was used. Nineteen per cent of the patients were found to be positive for enterobius. Brown, Sheldon and Thurston[9] examined 132 underprivileged white boys from Charlotte, N. C., and found 32 per cent of them to be infested with pinworms. In this series only a single NIH swab was used for each patient.

Many studies indicate that among institutionalized children the incidence of enterobiasis is even higher than among the general population. Sawitz and his associates[10] examined 491 institutionalized children in New Orleans by the NIH method and found the incidence of positives to be 74.3 per cent. According to their study, the incidence in children of comparable age was more than twice as high among those in large dormitories as among those in single or double rooms. Enterobius eggs were recovered from pajama pants, bed sheets, ledges, window sills, and door sills of dormitories and toilet rooms, indicating air vection. The National Institute of Health group[11] examined 106 children in a well-equipped, clean nursery school, the children ranging from 2 to 5 years of age. Fifty-five per cent of these children were positive by the NIH swab method.

Kuitunen-Ekbaum[12] found 70 per cent of the 140 children in a Toronto convalescent home to be positive. An average of 3.7 NIH swabs per child were made in this study. In another Canadian series[13] 198 French-Canadian school children were examined in the public school of a small community. Although only one NIH swab per child was made, 33 per cent of the children were positive.

Sawitz and co-workers[14] made a very careful study of 136 white children in a New Orleans institution. Repeated swabs were done in order to test the efficiency of the method. A total of 96.3 per cent of the children in this institution were found to have enterobiasis, although the first examination found only 70 per cent. They concluded that seven negative swabs were necessary before ruling out pinworm infestation.

The present study is based upon 228 unselected children seen as outpatients in the Children's Clinic of the Stanford University School of Medicine. The children ranged in age from 1 to 15 years and were chiefly white, with a few orientals and an occasional Negro. Each of these 228 children had one examination by the Scotch cellulose tape technique, and of this group, 72, or 31.3 per cent, were positive for enterobius. Of the 118 females in the group, 40, or 33.9 per cent, were positive; of the 110 males, 32, or 29.1 per cent, were positive. Two additional positives were found on a second examination and one additional positive on a third examination, making a total of seventy-five cases of pinworm infestation. However, not enough patients were examined more than once to warrant a further statistical study. If one applies the generally accepted statement of Sawitz and co-workers,[14] that the first examination with the NIH method finds 70 per cent of the positive cases, then about 45 per cent of the children in this group are infested with pinworms. This latter calculation may not be justified, however, since the relative efficiency of the NIH and the Scotch tape methods is not yet known.

It is of interest that in most instances in which more than one child of the same family came in for examination, all or most of the siblings were infested. In a few of these instances the parents submitted to examination and were also found to be positive. In this connection it is well to note the work of Nolan and Reardon,[15] who investigated the distribution of ova in household dust. They carefully collected dust specimens from seven homes in which a number of members had heavy pinworm infestations. In spite of the fact that six of the seven homes were clean homes by usual standards, 91.7 per cent of the 241 dust samples collected contained ova of pinworms. Many of these ova were incubated and hatched, thus proving viability. Viable ova were found at all levels in the room, even high on moldings and light fixtures.

SYMPTOMATOLOGY

Since it is obvious from the above data that enterobius infestation is a very widespread condition, the question immediately arises as to the results of such infestation on the patient. Faust[1] lists the symptoms of enterobiasis as follows: abdominal pain, pruritus ani, fretfulness, insomnia, urinary incontinence, masturbation, vaginal discharge, nymphomania, and loss of appetite. Brady and Wright[16] studied 200 cases of pinworm infestation both before and after treatment, relating the symptoms to infestation only if they cleared after treatment. They found infested children frequently to be underweight and to have pallid facies and dark circles under the eyes. As gastrointestinal symptoms, they list only anorexia and pruritus ani. Enuresis as a symptom of pinworms was doubtful, but vaginitis was frequent. Thirty-one per cent of the swabs from the introitus in pinworm-infested females were

positive. Nervous symptoms consisted of insomnia, restlessness, and constant scratching of the perianal region.

A study was made of the symptoms found in the present series of seventy-five cases of enterobiasis. The data presented are based upon symptoms elicited in the initial anamnesis. A post-treatment study of these same patients will be published at a later date along with an evaluation of therapy.

Of the seventy-five cases of enterobiasis studied, 49.4 per cent were termed "nervous" by their parent, 41.3 per cent complained of repeated attacks of abdominal pain, 41.4 per cent were underweight, 38.6 per cent had anorexia, 38.6 per cent were poor sleepers, 21.3 per cent had pruritus ani, and 17.3 per cent had enuresis. Of the forty females in the series, 27.5 per cent had vaginal discharge. During the period of this study, fourteen girls were seen in the Children's Clinic with a chief complaint of vaginal discharge, and 80 per cent of these were found to have oxyuris ova in both perianal and vulvar examinations. Many of these girls also complained of itching of the vulva. Of the seventy-five positive patients, 22.6 per cent had none of the symptoms mentioned, while 48.3 per cent of all the children examined had none of the symptoms mentioned.

The occurrence of abdominal pain has been striking. One case is especially interesting, since the patient suffered very frequent severe attacks of abdominal pain for which he had been hospitalized twice and had been subjected to two gastrointestinal x-ray series as well as excretory urograms. He has had no symptoms since the elimination of his pinworms. Many other patients have complained almost daily of "stomach-ache" but have had none since treatment with gentian violet enseals. More detailed follow-up on these cases will be reported in a later paper.

SUMMARY

1. A new technique for the diagnosis of enterobiasis has been discussed, and the results of the use of this technique on 228 unselected clinic children have been presented.

2. Of the 228 children, 31.3 per cent were positive for pinworm eggs.

3. Of the positive patients, 41.3 per cent had repeated abdominal pains, 49.4 per cent were "nervous," 41.4 per cent were underweight, 38.6 per cent were poor sleepers, 38.6 per cent had anorexia, 21.3 per cent had pruritus ani, and 17.3 per cent had enuresis.

4. Of the forty positive girls, 27.5 per cent had vaginal discharge. During the period of this study, fourteen girls were seen in the clinic with vaginal discharge. Eleven of them had oxyuris ova in both perianal and vulvar regions.

CONCLUSIONS

1. The Scotch cellulose tape technique is a simple and effective means of diagnosing enterobiasis.

2. Enterobiasis is a very common and much neglected disorder of childhood.

3. Vaginal discharge, attacks of abdominal pain, anorexia, undernutrition, insomnia, nervousness, enuresis, or pruritus ani should lead one to suspect enterobius infestation.

4. Enterobiasis is a common cause of vaginal discharge in childhood.

REFERENCES

1. Faust, E. C.: In Practice of Pediatrics, Joseph Brennemann, Editor, Hagerstown, Md., W. F. Prior Co., Inc., vol. 2, chap. 35, p. 8.
2. Hall, M. C.: Am. J. Trop. Med. **17:** 445, 1937.
3. Folan, J. P.: Pub. Health Rep. **54:** 1392, 1939.
4. Graham, C. F.: Am. J. Trop. Med. **21:** 159, 1941.
5. Reardon, Lucy: Am. J. Trop. Med. **18:** 427, 1938.
6. Cram, E. B., Jones, L., Reardon, L., and Nolan, M. O.: Pub. Health Rep. **52:** 1480, 1937.
7. Cram, E. B., and Reardon, L.: Am. J. Hyg. (Sect. D) **29:** 17, 1939.
8. Weller, T. H., and Sorenson, C. W.: New England J. Med. **224:** 143, 1941.
9. Brown, H. W., Sheldon, A. J., and Thurston, T.: South. M. J. **33:** 922, 1940.
10. Sawitz, W., D'Antoni, J. S., Rhude, K., and Lob, S.: South. M. J. **33:** 913, 1940.
11. Cram, E. B., and Nolan, M. O.: Pub. Health Rep. **54:** 567, 1939.
12. Kuitunen-Ekbaum, E.: Canad. Pub. Health J. **31:** 287, 1940.
13. Miller, M. J., and Choquette, L.: Canad. M. A. J. **43:** 453, 1940.
14. Sawitz, W., Odom, V. L., and Lincicome, D. R.: Pub. Health Rep. **54:** 1148, 1939.
15. Nolan, M. O., and Reardon, L.: J. Parasitol. **25:** 173, 1939.
16. Brady, F. J., and Wright, W. H.: Am. J. M. Sc. **198:** 367, 1939.

BONE DEVELOPMENT IN PRESCHOOL CHILDREN

CHARLES L. WILBAR, JR., M.D.
HONOLULU, T. H.

FOR ten years, a Health Project at Ewa, Hawaii, was occupied with studying the effect of diet upon the tooth decay and upon the general health of the preschool children living in the villages owned by the Ewa Plantation Company. During this time, the average population on this sugar plantation was approximately 4,000, with a mean of ninety-nine births per year. The effects of the diet of these children upon tooth decay and upon anemia have been previously published.[1, 2]

This paper deals with the findings of the roentgenograms of the wrists and ankles of these children and the relationship of dietary factors to these findings.

The influence of health and diet on osseous development has been stressed by Francis and Werle.[3] The Ewa children whose parents had been subjected to considerable health teaching during the ten years of the Project, with particular stress on diet, might therefore be expected to show a "normal" or accelerated rate of bone development. One indication of the good health of these children is the fact that the infant mortality rate at Ewa was under thirty per 1,000 live births for four out of the five fiscal years ending June 30, 1939.

FINDINGS

Three hundred and eighty-two films (8 by 10 inches) were exposed on 182 children of preschool age during 1936, 1937, and 1938. The films were exposed for one tenth of a second at a distance of thirty-six inches, using 100 Ma. and 50 KVP. Each film contained four exposures: an anteroposterior view of each wrist, and a lateral view of each ankle, including a portion of the distal ends of the long bones and a portion of the proximal ends of the metacarpals and metatarsals. These roentgenograms were taken chiefly for the purpose of determining the rate of bone development in the children under observation.

For comparison with the Ewa children, films were exposed on each of fourteen Hawaiian or part Hawaiian preschool children living in the Nanakuli homesteads on the same island and on each of thirty-one preschool children living on the nearby Waialua Plantation. The racial backgrounds of the children at Ewa and at Waialua are similar. Approximately two-thirds of the children studied at each of these plantations were of Japanese origin and one-third of Filipino origin. There was an occasional Portuguese or other Caucasian child.

From the Queen's Hospital Research Department.

Authorities differ considerably as to the exact normal time of appearance of osseous centers.[3-6] Compared with the table for Range of Appearance of Osseous Centers of Extremities prepared by the Harvard School of Public Health (range of middle 50 per cent), seventy-two out of the 182 Ewa children showed a retardation beyond normal limits of the appearance of their osseous centers at some time during the three-year study, and none of them had an accelerated rate of development.

Using a modification of the diet analysis developed by Burke and Stuart at the Harvard School of Public Health,[7] a determination was made of the diet of the Ewa children included in this study. The changes from the original method of diet analysis consisted of including Hawaiian foods and cross-questioning the mothers more thoroughly about details of their children's diets, using a sample set of standard household measures and sample blocks of wood of known volume to check against the volumetric judgment of the mothers. Quantitative determinations were made of the intake of the various food elements in each child's diet.

Calcium, phosphorus, vitamin D, and vitamin A have been named by various authors as concerned in osseous development.[8-13] The vitamin D intake of the Ewa children could not be ascertained with any degree of accuracy because of their heavy exposure to sunshine. The work of Venar and Todd[11] would indicate that this vitamin is not such an important factor in determining the extent and density of mineralization of growing bone as was believed. Since there is an average of only about twenty inches of rain per year at Ewa, with better than seven and one-half hours of sunshine per day on the average, and the climate is conducive to having children play out-of-doors during all of the year (which they do), there would seem to be little doubt that the Ewa children receive optimum amounts of vitamin D. Further indication of adequate vitamin D in these children is the paucity of evidence of rickets in the x-rays of these children and complete absence of clinical evidence of rickets. Fifteen of the 182 showed questionable x-ray signs indicative of mild rickets. Two of the Nanakuli group and one of the Waialua group showed similar signs.

Of the seventy-two children in the group studied at Ewa who showed retarded osseous development by comparison with the table developed by the Harvard School of Public Health, satisfactorily accurate dietary histories were obtained in fifty-nine cases. The remaining histories were omitted from statistical analyses because of insufficient cooperation or ignorance on the part of the parents, change of residence before completion of the history, sickness, etc.

A mean of 1.35 Gm. of calcium per day was eaten by these children, with a probable error of the mean of ± 0.14. Thus they were obtaining in their diet an amount of calcium close to, but in most cases definitely more than, the 1.0 Gm. considered to be a minimum adequate intake for children of this age group by the Committee on Foods and Nutrition of the National Research Council.[14]

Their mean phosphorus intake was 1.31 Gm., with a probable error of the mean of ±0.12, as compared with an adequate ingestion of this mineral of about 1.2 Gm.[15]

The vitamin A ingested daily by these children was a mean of 6,580 I. U., with a probable error of ±330 units.

Thus, in considering the factors in the diet of this group of children which might affect their osseous development, it would seem that they received sufficient amounts of vitamins A and D and sufficient amounts of calcium and phosphorus, close to an adequate intake, even though the osseous development in seventy-two cases was below "normal."

The entire 182 children at Ewa who were studied showed a mean daily vitamin A intake of 6,320 I. U., a mean calcium daily intake of 1.02 Gm. and a mean phosphorus intake of 1.10 Gm.

There was, then, no significant difference between those children with retarded osseous development and those with normal development as far as the intake of vitamin A, calcium, and phosphorus was concerned. Since it can well be assumed that all of them received adequate vitamin D also, it would seem that none of these four food factors under suspicion, in the amounts ingested, were concerned in causing retarded development among the children in this group.

None of the fourteen Nanakuli children showed retarded development, and three of them showed appearance of osseous centers sooner than the range of the middle 50 per cent of the Harvard School of Public Health tables. The speed of the bone development of the Nanakuli children may be due to the fact that they were of Hawaiian extraction or due to the diet of the children. Their diet was not supervised or analyzed as was that of the Ewa children. Inquiry into their eating habits, however, revealed that they were eating large quantities of poi, the favorite food of the old Hawaiians, which is made from the tuber of the taro plant. Several 2-year-old children were discovered to be consuming three bowlfuls of poi, or about one pound of this pasty food, per day. Poi is rich in calcium, phosphorus, and vitamin B_1.[16, 17] These children, like other Hawaiian children in the Territory living in rural areas and eating largely the diet of their forebearers, also ate large quantities of sea food, including many opihi, a common shellfish which has been shown by the nutrition laboratory of the University of Hawaii to contain as much vitamins A and D as good cod-liver oil.[17] Opihi is also high in calcium. Nanakuli and Ewa have equally scant rainfall. Consequently, the Nanakuli children also receive optimum amounts of sunshine. Thus, these children, whose diet seemed to be otherwise "well balanced" as far as questioning of their mothers revealed, were actually receiving excessive amounts of vitamins A and D and large quantities of calcium and phosphorus. Because these factors accompanied the speedy bone development in these children, however, does not necessarily lead to a conclusion of cause and effect.

Five of the thirty-one Waialua children showed retarded osseous development by the same criteria. The children on the Waialua Plantation live under practically the same conditions as those on the Ewa Plantation. An attempt to analyze the diet of the Waialua children with accuracy was not successful. They were not subject to the same dietary teaching and control as the Ewa children, and, in general, ate a substandard diet.

An interesting finding in the majority of the films of all of the children in the three locations was an increased density at the distal metaphyses of the long bones. These opaque bands varied considerably in thickness and density, but no relation could be ascertained between them and illness, heavy metal poisoning, rickets, or endocrine imbalance. In fact, the most healthy children, who had never experienced an illness and whose x-rays showed normal osseous development, were the ones in whom these opacities were most often found. Some of the films showing these terminal bands of density in the long bones were reviewed by the Philadelphia Roentgen Ray Society, by Ingber, Kile, and Rodenbaugh, San Francisco roentgenologists, and by Dr. Harris, of London. These physicians felt that this finding was evidence of a disturbance in bone metabolism but was seen frequently enough in healthy children to be within normal limits. Todd[18] has suspected similar markings to be due to gastrointestinal allergy. Sontag and co-workers[19, 20] suggest prenatal influences and emotional factors among other possible causes.

These opacities can hardly be considered normal and without significance since they do not appear in all children. Further investigation of their etiology would seem to be indicated.

DISCUSSION

This investigation discovered preschool children with retarded bone development compared to a table of "normal" based on broad bands. The retardation was present in spite of an adequate intake of the food factors believed to be necessary for proper bone development, according to generally accepted dietary standards. These findings would tend to throw suspicion on one of the two sets of "normal" standards, either the standard concerned with food elements or that concerned with osseous development.

There is much lack of agreement among various authors as to what constitutes normal bone development. Besides diet, sex, and general health, it is probable that such factors as racial extraction and hereditary body build need to be considered. The naturally small Filipino on a good diet does not begin to approach in size the Hawaiian eating a nutritious diet, and it is hard to conceive that generations of proper feeding would ever bring these two racial types to the same stature. Indeed, the meager nutritional evidence obtainable from the Philippines tends to indicate that the diet of the Filipino in his natural habitat has

been adequate from a nutritional standpoint, though his stature has always been small. With osseous development apparently influenced by these various factors, it would seem that we should be most hesitant in attempting to determine chronologic age accurately from a comparison of bone development in any individual with "normal" standards.

Although much research has been done in the field of nutritional standards in recent years, these standards are yearly being changed by leading authorities. The rapid metabolic rate of the preschool child, with its many marked individual variations among children in good health, makes minimum standards for nutritional elements in this period difficult of determination and requires many more observations than are yet available.

SUMMARY

1. Roentgenograms of both wrists and both ankles of 182 preschool children of Japanese and Filipino origin, living at Ewa Plantation, were taken through the Ewa Health Project for three consecutive years.

2. For comparison, similar films were made of fourteen Hawaiian or part Hawaiian preschool children living nearby and of thirty-one preschool children of Japanese and Filipino origin living on another sugar plantation on the same island.

3. Seventy-two out of the 182 Ewa children showed retarded osseous development at some time during the 3-year period of the study, and none showed an accelerated rate of development, using as a criterion the table for Range of Appearance of Osseous Centers of Extremities prepared at the Harvard School of Public Health. From other types of examinations and mortality rates, this group of children had an exceptionally good health record.

4. None of the Nanakuli control children showed retarded osseous development, and three of them showed acceleration of development over the "normal." These children, besides being Hawaiians, received an excess of vitamins A and D and large quantities of calcium and phosphorus in their dietary.

5. Five of the thirty-one control children at Waialua showed retarded osseous development. Their diet, though not analyzed carefully, did not in general meet minimum standards of adequacy.

6. An analysis was made of the diets of the Ewa children, with resultant quantitative determinations of the food elements in their dietary.

7. A comparison of the intake of the Ewa children of vitamins A and D, of calcium and phosphorus, with standard tables of requirements of these food elements shows an adequate ingestion of these four elements which have been under suspicion as affecting bone development, both for those children showing retarded bone development and for the remainder of the Ewa group.

8. A majority of the children at all three locations showed opacities at the distal ends of the long bones. Most of these opacities were found

in children who had always been in good health. Studies of these films by various roentgenologists, and of this condition elsewhere, have failed to uncover the etiology of these opacities.

CONCLUSIONS

Since tables of bone development show wide variations in the "normal," there might be some question as to their accuracy as gauges of the health of the growing child. However, this study would tend to indicate one of three conclusions: (1) There is an as yet unrecognized racial or hereditary factor which has to do with bone development; or (2) standards of adequate intake of calcium, phosphorus, vitamin A and/or vitamin D should be raised; or (3) retarded osseous development is an exceptionally fine indicator of inadequacies in diet.

The author is indebted to A. L. Y. Ward for the painstaking efforts necessary for the collection of accurate information concerning the diet of the Ewa children.

REFERENCES

1. Larsen, N. P., Jones, M. R., and Pritchard, G. P.: Am. J. Dis. Child. **48**: 1228, 1934.
2. Wilbar, C. L.: Am. J. Dis. Child. **58**: 45, 1939.
3. Francis, C. C., and Werle, P. P.: Am. J. Phys. Anthropol. **24**: 273, 1939.
4. Vogt, E. C., and Vickers, V. S.: Radiology **31**: 441, 1938.
5. Kohler, Alban: Roentgenology.
6. Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, 1937, The C. V. Mosby Co.
7. Burke, B. S., and Stuart, H. C.: J. PEDIAT. **12**: 493, 1938.
8. Francis, C. C.: Am. J. Dis. Child. **57**: 816, 1939.
9. Outhouse, J., Smith, J., Merritt, L., and White, F. R.: J. Nutrition **14**: 589, 1937.
10. Adams, C. O.: Proc. Soc. Exper. Biol. & Med. **38**: 449, 1938.
11. Venar, Y. A., and Todd, T. W.: J. Lab. & Clin. Med. **22**: 221, 1936.
12. Yudkin, A. M.: J. PEDIAT. **12**: 701, 1938.
13. MacNair, V.: Am. J. Dis. Child. **58**: 295, 1939.
14. Bureau of Home Economics Bulletin, U. S. Department of Agriculture, July, 1941.
15. Sherman, Herman C.: Chemistry of Food and Nutrition, New York, 1941, The Macmillan Co.
16. Miller, C. D.: B. P. Bishop Museum Bull. 37, 1937, Honolulu.
17. Report of the Hawaii Agricultural Experiment Station, 1936, Honolulu.
18. Todd, T. W.: Am. J. Dis. Child. **55**: 156, 1938.
19. Sontag, L. W., and Harris, L. M.: Am. J. Dis. Child. **56**: 1248, 1938.
20. Sontag, L. W., and Comstock, G.: Am. J. Dis. Child. **56**: 301, 1938.

TETANY IN THE NEWBORN INFANT

EDWIN L. KENDIG, JR., M.D.
RICHMOND, VA.

TETANY in the newborn infant is not uncommon. In 1939 Bakwin[1] was able to assemble from the literature twenty-seven cases, including four of his own. Since that time at least one other has been added.

The danger of a convulsion during the neonatal period cannot be overstressed. Because tetany in the newborn infant is probably more frequent than is generally realized and because there exists, in calcium, a therapeutic agent for it, the following four cases observed by me are reported.

CASE 1.—R. K., a boy, was delivered by a midwife on Jan. 16, 1939. There was some difficulty in resuscitating the child. The efforts of the pulmotor squad were successful, but respirations continued to be irregular. At the time of admission to Bellevue Hospital, the baby was cyanotic and breathing slowly and irregularly. There were no other abnormal findings.

On the day after admission, the baby was considerably improved. He weighed 7 pounds, 8 ounces. His cry was vigorous, and the respirations were regular although shallow. There were no abnormal neurologic signs. The feeding, consisting of a whole milk formula with dextrimaltose, was taken well.

Two days after admission, the child had a generalized convulsion which lasted ten minutes, and he remained spastic several minutes thereafter. The convulsion was controlled by sodium bromide and chloral hydrate, and a regimen of sodium luminal, ⅛ gr. every four hours as needed, was instituted. The cerebrospinal fluid was crystal-clear, and both microscopic and chemical examinations were negative. The serum calcium was 7.6 mg. per 100 c.c. Calcium gluconate (10 c.c. of a 10 per cent solution) was given intramuscularly, and a regimen of calcium lactate, 15 gr. every four hours, by mouth was begun. By the end of that same day the infant had had a total of seven generalized convulsions, two occurring after administration of 15 gr. of calcium intramuscularly and 15 gr. by the oral route. At no time was there a positive Chvostek, peroneal, or Trousseau sign, and there was no carpopedal spasm.

On the following day, the child was much improved and took his formula well. There were no more convulsions and the serum calcium was 9.6 mg. per 100 c.c. Four days later the serum calcium had risen to 10.6 mg. X-rays of the long bones and of the skull were negative. Eleven days after admission, the child, then weighing 8 pounds, was discharged in good condition. Attempt at follow-up was unsuccessful.

CASE 2.—M. K., a boy, was born at Bellevue Hospital on Feb. 12, 1939, at full term and weighed 6 pounds, 15 ounces. The patient was the second child, and the sibling was alive and well. Delivery of the patient was accomplished by means of

From the Department of Pediatrics, New York University, the Children's Medical Service of Bellevue Hospital, New York City, and the Department of Pediatrics of the Medical College of Virginia Hospital, Richmond.

low forceps after the mother had been in labor for three and one-half hours. Pregnancy was complicated by placenta previa. There was some difficulty in resuscitating the child.

The baby was apparently well until the third day of life when he had a generalized clonic convulsion lasting five minutes. This recurred on two occasions shortly thereafter. After cessation of the generalized convulsions, muscular twitchings persisted. The baby was stuporous and could not be roused. Respirations were regular but shallow, with some retraction of the lower ribs. The only other abnormal findings were a positive peroneal and a positive Chvostek reaction. The cerebrospinal fluid was xanthochromic (there is no further information as to the cerebrospinal fluid findings). Serum calcium at this time was 7.1 mg. per 100 c.c. A regimen of calcium chloride, 15 gr. every four hours, by mouth was begun, and after twenty-four hours the same calcium dosage was administered in the form of lactate and continued for six days. There were no further convulsions after the institution of calcium therapy. Serum calcium, taken two days after calcium treatment was begun, was 9.8 mg. per 100 c.c.

From the time of diagnosis the baby was fed only breast milk. The baby was discharged in good condition seven days after admission. He weighed 7 pounds, 3 ounces at that time.

CASE 3.—D. T., a girl, was delivered at the Medical College of Virginia Hospital on Oct. 19, 1941, and weighed 5 pounds, 14 ounces. The patient was the third child, and the siblings were alive and well. The mother had had daily dosage of calcium, 15 gr., and vitamin D, 660 I.U., throughout the last six months of pregnancy. Delivery of the patient was effected spontaneously from a vertex L.O.A. presentation after a labor of four hours and fifty minutes. Resuscitation of the child was not difficult. She was given vitamin K intramuscularly as part of routine.

A day or two after birth the baby exhibited marked hyperexcitability. There were occasional attacks of twitching of one or more of the extremities. The baby frequently vomited her formula. Physical examination, when she was 7 days of age, revealed a marked hyperexcitability but no abnormal neurologic signs. Twenty-four hours later, serum calcium was found to be 5.6 mg. per 100 c.c. Fifteen grains of calcium lactate were given every four hours for two days, at which time the patient was discharged in good condition. The infant did not seem to be particularly excitable at this time, and there were still no abnormal neurologic findings. Another serum calcium determination was not made.

CASE 4.—S. B., a girl, was delivered at the Medical College of Virginia on March 31, 1942. This was the mother's first pregnancy, and she took calcium, 15 gr., and vitamin D, 660 I.U., "irregularly" for the last six months of pregnancy. Pregnancy was complicated by partial premature separation of the placenta, and labor was induced. The patient was delivered by means of low forceps from a vertex L.O.A. presentation after a labor of twelve hours and fifty-one minutes. Vitamin K was given to the baby as part of routine. The patient weighed 6 pounds, 14 ounces, and showed a partial paralysis of the left side of the face. She also exhibited some hyperexcitability, but otherwise was in good condition until the eighth day of life. At that time she had a generalized convulsion, lasting about one minute. Physical examination showed a positive Chvostek and a positive peroneal reaction. Serum calcium was 6 mg. per 100 c.c. Lumbar puncture was unsuccessful. Calcium gluconate, 15 gr. every four hours, by mouth was begun, but during the ensuing twelve hours the baby had three more generalized convul-

sions. It was then discovered that, due to a technical difficulty, the patient had received only about 30 gr. of calcium during this period. This was corrected and the course thereafter was uneventful. Another calcium determination was not made.

DISCUSSION

Tetany may occur at any time during the newborn period. It is seen in full-term as well as premature infants and affects both males and females in equal number.

The pathogenesis of tetany in the newborn is still a source of contention. According to Bakwin,[2, 3] tetany in the newborn infant is attributable to parathyroid deficiency. He has been able to show that during the early days of life there exists a state of physiologic hypoparathyroidism, analogous to the physiologic hypoprothrombinemia associated with hemorrhagic disease. The hypoparathyroid individual is sensitive to phosphate injection or ingestion, responding with hypocalcemia. Bakwin believes that any condition which releases phosphorus endogenously, as in the excessive starvation associated with cerebral injury, or administration of cow's milk, which contains large amounts of phosphorus, may precipitate tetany in the newborn infant.

The clinical picture of tetany in the newborn infant is not a specific one. The diagnosis should be suspected whenever there is a convulsion, twitching, or abnormal hypersensitivity. The symptoms and signs, however, may be duplicated by intracranial hemorrhage or congenital cerebral defect. The diagnosis of tetany in the newborn infant is made when the serum is below 8 mg. per 100 c.c. The serum phosphorus is ordinarily elevated but it may be unchanged. The serum phosphatase, unlike that in tetany of later infancy, is not changed. Craniotabes may be present, but evidence of rickets is not otherwise demonstrable.[4]

Prompt and permanent relief can be effected by the administration of calcium. If the convulsions are severe or continuous, calcium gluconate (5 to 10 c.c. of a 10 per cent solution) should be given intravenously. If the symptoms are less severe, a satisfactory result may be obtained by oral administration. Fifteen grains of calcium gluconate, bromide, or lactate every four hours should be given for two to three days. Intramuscular administration of calcium to newborn infants should be avoided, since abscess formation not infrequently follows.

Treatment by agents other than calcium is unsatisfactory. Vitamin D preparations are ineffective. The dosage of parathormone is difficult to gauge; furthermore, it acts by removing calcium from already depleted endogenous stores. Bloxsom[5] has reported a case of tetany in the newborn infant successfully treated with dihydrotachysterol, but this drug is not as readily available as is calcium, and the dosage is not easily gauged.

When treated promptly the prognosis is good.

SUMMARY

Tetany may occur at any time during the newborn period. It should be suspected whenever hypersensitivity, twitching, or a convulsion occurs in a newborn infant. Diagnosis is made when the serum calcium is below 8 mg. per 100 c.c. Calcium is a specific therapeutic agent. Four proved cases are reported.

REFERENCES

1. Bakwin, H.: J. PEDIAT. **14**: 1, 1939.
2. Bakwin, H.: Am. J. Dis. Child. **54**: 1211, 1937.
3. Bakwin, H.: Personal communication.
4. Holt, L. Emmett, Jr., and McIntosh, Rustin: Diseases of Infancy and Childhood, ed. 11, New York, 1940, D. Appleton-Century Co., Inc., p. 90.
5. Bloxsom, A.: J. PEDIAT. **16**: 344, 1940.

1214 WEST FRANKLIN STREET

THE WELTMANN REACTION IN RESPIRATORY DISEASES IN CHILDREN

SUSAN C. DEES, M.D., DURHAM, N. C., AND
HENRY MORTON, M.D., SARASOTA, FLA.

THE Weltmann serum coagulation reaction has been determined in 500 children in whom a definite clinical or pathologic diagnosis was made. One hundred and fifty-eight or nearly one-third of these cases were common respiratory diseases, nasopharyngitis, tonsillitis, acute bronchitis, pneumonia, and bronchial asthma. Fig. 1 shows that acute infections of any type have coagulation bands from zero to four, less severe infections have bands from four to six, and chronic infections have bands from six to ten. In the latter group a few exceptions are encountered; namely, nephrosis, leucemia, and necrotic tumors. This paper will consider only the patients with respiratory infections. The technique* for performing the test and the theoretical aspects of it are described in detail elsewhere.[1-3]

The coagulation bands in thirty-two cases of nasopharyngitis are shown in Fig. 2. Twenty-two cases had bands of five, eight had bands of four, and two had bands of six. All of the patients with bands of five and six had uncomplicated upper respiratory infections. Those with bands of four had additional mild infection of skin, middle ear, or cervical lymph nodes. Leucocytosis and temperature did not parallel each other and could not be used as a basis for separating the complicated cases from the uncomplicated. The white counts in both groups ranged from 3,000 to 15,000 and the temperature from 36.5 (97.6° F.) to 38.7° C. (101.8° F.).

The distribution of the coagulation band in forty-six patients with tonsillitis is shown in Fig. 3. The patients with acute tonsillitis had coagulation bands from two to four, those with chronic tonsillitis from four to seven. The only overlapping occurred in the band of four in which were thirteen acute and four chronic infections. In tonsillitis there was even wider variation in white count and temperature than in simple upper respiratory infections. In acute tonsillitis the white blood counts ranged from 5,000 to 30,000 and the temperatures from 37.5 (99.5° F.) to 38.7° C. (101.8° F.) were observed. In general, the patients with acute infections had high temperatures and leucocytosis, but there was so much individual variation that neither white count

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital, Durham, N. C.

*Two and five-tenths cubic centimeters of $CaCl_2$. 6 H_2O in dilutions ranging from 0.1 to 0.01 per cent are measured into ten small test tubes numbered from one to ten to correspond with the dilutions, beginning with the most concentrated. Five-hundredths of a cubic centimeter of unhemolyzed serum is added and mixed in each tube. The tubes are then immersed in a boiling water bath for fifteen minutes. The number of tubes showing coagulation indicates the length of the coagulation band. Normal unhemolyzed serum has a coagulation band of six.

nor elevated temperature could be used as a criterion for distinguishing the acute from chronic cases. There are borderline cases, particularly of chronic tonsillitis, in which the activity of infection is not easy to determine. In these patients the Weltmann reaction is of real assistance, since a coagulation band of four represents considerable infection, whether it is acute or chronic. The length of the coagulation band will often give a clue as to which of the other findings are reflecting the disease process most accurately.

Fig. 1.—Range of coagulation band in different types of diseases.

The group of thirty-eight patients with lobar pneumonia, bronchopneumonia, unresolved pneumonia, and acute bronchitis are presented together in Fig. 4. None of the eighteen patients with lobar pneumonia had coagulation bands longer than zero at the onset or early in the disease. Thirteen patients with bronchopneumonia had bands from zero to four. Five cases of acute bronchitis had coagulation bands from two to five. Four patients with incompletely resolved pneumonia three weeks to three months after their acute illness all had coagulation bands of five. The values for the entire group are in accord with reports in the literature.[4] The clinical course and laboratory findings in one of the patients with lobar pneumonia are shown in Fig. 5. The progressive rise in the Weltmann reaction was helpful in excluding empyema, since this trend

was not compatible with the presence of a large accumulation of pus. The physical signs throughout the patient's hospital admission were dullness to flatness and absent breath sounds over the entire left chest.

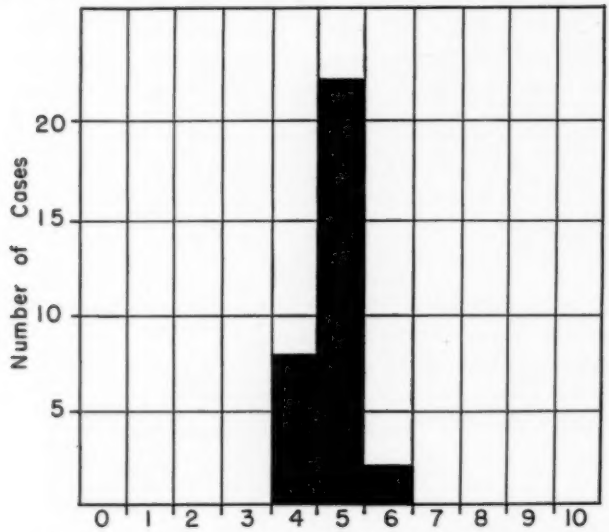


Fig. 2.—Distribution of coagulation band in thirty-two cases of upper respiratory infection.

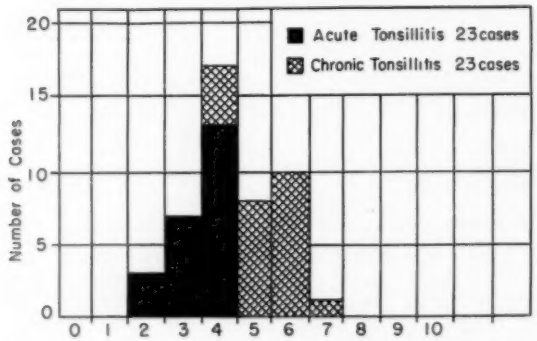


Fig. 3.—Coagulation band in forty-six cases of acute and chronic tonsillitis.

Chest x-ray showed dense clouding of the entire left chest which remained stationary until the end of the second week. Repeated thoracenteses yielded no fluid. Spinal fluid, blood and urine cultures were negative. The white count and temperature fell steadily after the first forty-eight hours, but they were still definitely elevated at the twelfth day.

The clinical course and laboratory findings in the thirteen cases of bronchopneumonia are summarized in Table I. The duration of illness

varied from one to twenty-one days at the time the Weltmann reaction was done. Only three cases were uncomplicated. The others followed measles, foreign body, operation, or were associated with nephritis, heart disease, or some focus of infection. One child, who was moribund

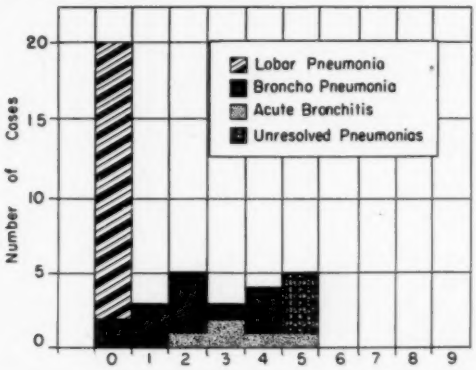


Fig. 4.—Coagulation band in thirty-eight cases of pneumonia.

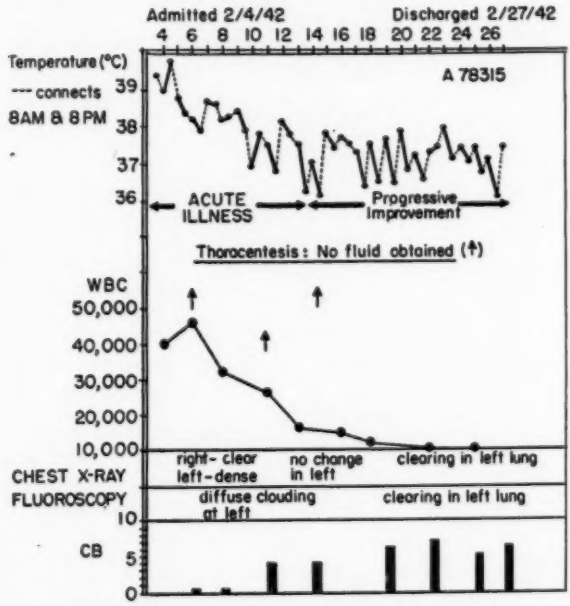


Fig. 5.—Clinical course of severe lobar pneumonia.

on admission, had interstitial pneumonia. All of the patients were treated with sulfathiazole or sulfapyridine. It is well known that the sulfonamides may alter white count and temperature, but they apparently do not influence the Weltmann reaction. The coagulation band

TABLE I

CLINICAL AND LABORATORY FINDINGS IN THIRTEEN PATIENTS WITH BRONCHOPNEUMONIA

HISTORY NUMBER	AGE	DAY OF ILLNESS	COAGULATION BAND	WHITE BLOOD COUNT	TEMPERATURE °C.	X-RAY	DIAGNOSIS	R*	RESULT
A25917	3 yr.	8	0	8,940	37.2	Bilateral diffuse increase lung markings	Bronchopneumonia; purulent otitis media	St.	Improved
A52797	11 mo.	3 8 10	0 0 0	30,000 11,320 9,250	40.3 37.2 37.4	Bronchopneumonia, right Discharge; lungs almost clear	Bronchopneumonia	St.	Afebrile in 40 hours; uneventful recovery after twentieth day of illness
A68892	6 yr.	1	1	20,800	39.4	Circumscribed lesion, right upper lobe	Postoperative bronchopneumonia	St.	Recovery
A24818	16 mo.	3 5	1 3	15,900 13,100	40	Early bronchopneumonia, right	Bronchopneumonia; hypothyroidism	Sp.	Improved; râles in chest on discharge fifteenth day of disease
A54400	2 yr.	1 wk.	1	20,000	40.5	Consolidation, right lower lobe	Bronchopneumonia; measles	St.	Improved
A54827	21 mo.	7	2	28,000	38	Bilateral extensive bronchopneumonia	Neurodermatitis 6 mo.; gangrene fingers, toes; bronchopneumonia; terminal lipoid pneumonia	Sp.; St.; vitamins	Death on twenty-eighth day of illness; autopsy

A54834	9 mo.	21 29	2 4	26,000 11,250	38.1 37		Pyarthrosis shoulder; pertussis; postoperative bronchopneumonia	St.	Death; no autopsy
A49404	3 mo.	7 9	2 4	15,600	37.8 37.8	Central pneumonia, right lung	Bronchopneumonia	Sp.	Unresolved pneumonia 3 months later
A54959	9 mo.	12	2	11,920	40	Extensive patchy bronchopneumonia, right	Bronchopneumonia	St.	Afebrile 48 hours, second spike in temperature, 39°, on fourteenth day; subsequent uneventful recovery
A73644	3 yr.	14	3½	13,200	37.3	Bronchopneumonia; enlarged heart	Acute nephritis; bronchopneumonia	St.	Discharged after 10 days; lungs clear; improved
72868	5 yr.	1	4	20,000	40	Increased peribronchial markings (on discharge)	Bronchopneumonia; mongolism; congenital heart disease	St.	Improved on ninth day of disease
A74168	7 yr.	3	4	24,900	38	Bilateral bronchopneumonia	Extensive bilateral interstitial bronchopneumonia; moribund on admission	St.	Death in 7 hours; autopsy
A54205	2 yr.	11	4	17,100	38	Diffuse miliary consolidation, right lung, left hilum	Bronchopneumonia, secondary to foreign body (hematuria and anemia due to sulfapyridine)	Sp.; S. diaz.; bronchoscopy	Recovery after forty-one days

*℞—St., sulfathiazole; sp., sulfapyridine; s. diaz., sulfadiazine.

was frequently short after patients had made striking clinical improvement. The three fatal cases had coagulation bands of two to four on admission. Their white counts were 28,000, 26,000, and 24,900 respectively, and all had temperatures of 38° C. (100.6° F.). There were prompt recoveries in patients who had leucocytosis as high as 30,000 with temperatures of 40.3° C. (104.6° F.) and whose coagulation bands were both shorter and longer than in the fatal cases. None of the laboratory tests or isolated clinical findings can be relied upon alone to give an accurate prognosis in bronchopneumonia. The Weltmann reaction can be useful in suggesting the presence of bronchopneumonia as a complication of other diseases of the respiratory tract, aspirated foreign bodies, and in postoperative cases which do not have shortened bands.

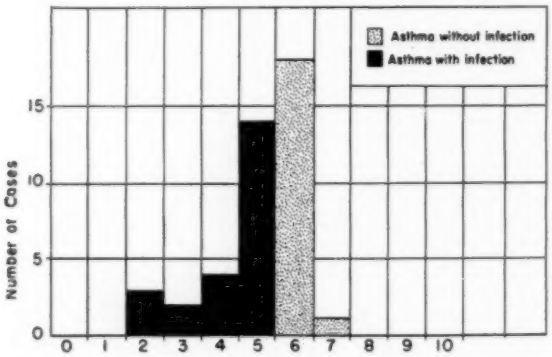


Fig. 6.—Coagulation band in forty-two cases of asthma.

The Weltmann reaction in forty-two children with bronchial asthma are shown in Fig. 6. One-half of the group was free from any infection, and without exception had bands of six. The remainder had a variety of complicating infections, varying from capillary bronchitis to chronic tonsillitis. These children had bands of from two to five. The white count and temperature are so frequently elevated in acute allergic episodes not due to infection that they are of relatively little value in determining the presence of infection. The sedimentation rate is often abnormally slow in allergic individuals. When infection and allergy are both present in an allergic person, the sedimentation rate may not give an accurate indication of the activity of infection. The Weltmann reaction has the definite advantage of being uninfluenced by the allergic state itself, and at the same time it is sensitive to the presence of even small degrees of infection. Any deviation of the Weltmann reaction from the normal coagulation band of six is significant. X-rays of the chest are important in the diagnosis and examination of an asthmatic child, but the interpretation of increased peribronchial marking in such a patient may be extremely difficult without previous

plates for comparison. In Table II the clinical and laboratory data in twenty of the cases of bronchial asthma are summarized. These patients were selected from the entire group because their chest x-rays showed comparable degrees of peribronchial fibrosis. It will be noted that some of these patients were acutely ill with upper respiratory tract infections, others were in acute asthmatic attacks, while others were

TABLE II

COMPARISON OF COAGULATION BAND, SEDIMENTATION RATE, AND WHITE BLOOD COUNT IN TWENTY CASES OF BRONCHIAL ASTHMA

(CHEST X-RAYS SHOWED COMPARABLE DEGREES OF PERIBRONCHIAL FIBROSIS)

HISTORY NUMBER	COAGULATION BAND	WHITE BLOOD COUNT	CORRECTED SEDIMENTATION RATE MM./HR.	TEMPERATURE °C.	ADDITIONAL FINDINGS
96690	2	15,950	17	38	Acute bronchitis
A53304	3	9,200	23	37.4	Chronic tonsillitis and adenoiditis, Tuberculin +
A67916	3	10,450	26	37.8	Acute bronchitis
	6*	8,600	23	37	Continuous asthma 3 months
A51268	4	6,800	10	37.8	Capillary bronchitis
A53473	4	15,750	21	36.6	Chronic bronchitis
A46489	5	10,050	21	37.2	Chronic tonsillitis and adenoiditis
A53875	5	10,000	5	37.7	Acute antral sinusitis
A53621	5	13,300	Below 1	36.2	Acute pharyngitis
A52362	5½	8,500	12	37.5	Subsiding upper respiratory infection
					Chronic tonsillitis and adenoiditis
A53472	5	6,700	16	36.4	Chronic tonsillitis and adenoiditis
A69433	5	6,350	40	36.4	Chronic tonsillitis and adenoiditis, urticaria and angioneurotic edema
A74141	5	11,360	10	37	Chronic tonsillitis and adenoiditis; eczema
A71415	6	7,550	17†	37	Asymptomatic
A71134	6	10,000	9†	37.7	Asymptomatic
A73828	6	10,150	20	35.9	Asthmatic attack
A69703	6	7,700	20	37	Mild asthma
A69178	6	7,800	3	37.2	Angioneurotic edema
A57272	6	14,000	5	37.4	Eczema
A55463	6	10,650	0	36.3	Subsiding asthmatic attack
A56080	6	6,760	11†	37.6	Acute asthmatic attack

*Same patient four days later.
†Uncorrected sedimentation rate.

asymptomatic at the time of examination. Both high and low white counts and sedimentation rates were observed in some of the patients in the complicated and uncomplicated groups. An increased sedimentation rate was not regularly associated with leucocytosis. There was very little elevation of temperature in the children with infection and shortened coagulation bands, but slightly lower temperatures were noted in the children without infection and with bands of six. Similar observations in adult asthmatic patients lead us to conclude that the Weltmann reaction is remarkably reliable in detecting infection in bronchial asthma.[5]

DISCUSSION

The Weltmann serum coagulation reaction has certain highly desirable features as a laboratory test. Among these are a constant value in normal healthy persons, and a definite range of deviation in known pathologic processes such as acute infection. It is unaffected by many of the nonpathologic and physiologic factors, for example, dehydration, acidosis, and alkalosis, which influence the white count and temperature. Infection alters the Weltmann reaction to exactly the same extent in allergic and nonallergic persons. Factors which may modify the sedimentation rate, such as anemia and allergy, are not considerations in interpreting the Weltmann reaction.[6] The test has the advantage of being simple to perform and gives consistent results if accurate dilutions and unhemolyzed serum are used. The coagulation band can be read within twenty minutes after a sample of serum is obtained. Several Weltmann reactions can be done in essentially the same length of time as one determination and much more rapidly than an equal number of sedimentation rates. The micromethods which have been described require very little blood and do not necessitate venipuncture, but they do require apparatus which is not standard in all laboratories.[7, 8] One point which should be stressed is that a change in the Weltmann reaction of one tube is of definite significance in interpreting the reaction. The value of the test will increase as it is used more widely and as coagulation bands are determined for a wide variety of diseases. The Weltmann reaction will continue to retain its principal disadvantage of nonspecificity until the fundamental mechanism governing the coagulation of serum proteins under these special conditions is understood.

SUMMARY

1. The Weltmann serum coagulation bands have been determined in a series of 500 pediatric patients in whom an accurate clinical or pathologic diagnosis was made.

2. The coagulation band is shortened below the normal value of six in the presence of infection and is increased with recovery.

3. In mild respiratory infections the coagulation band is slightly shortened; values of four and five are found.

4. In lobar pneumonia, at the onset, the coagulation band is zero and remains low until recovery is well established.

5. Bronchopneumonia has no characteristic band; the values range from zero to four.

6. In bronchial asthma the coagulation band is six unless there is some coexisting infection, which shortens the band.

7. The clinical condition and laboratory findings are compared with the Weltmann reaction in bronchopneumonia and bronchial asthma.

8. The use of the Weltmann reaction as a laboratory test in detecting and estimating activity of infection has again been stressed.

REFERENCES

1. Weltmann, O.: Med. Klin. **26**: 240, 1930.
2. Dees, S. C.: J. PEDIAT. **17**: 44, 1940.
3. Dees, S. C.: J. PEDIAT. **17**: 53, 1940.
4. Levinson, S. A., Klein, R. I., and Rosenbloom, P.: J. Lab. & Clin. Med. **23**: 53, 1937.
5. Dees, S. C.: South. M. J. **34**: 586, 1941.
6. Levinson, S. A., and Klein, R. I.: Ann. Int. Med. **12**: 1948, 1938.
7. Kling, D. H.: J. Lab. & Clin. Med. **26**: 1795, 1941.
8. Szante, Paul B., and Oxman, E.: J. Lab. & Clin. Med. **27**: 94, 1941.

POSSIBLE HAZARDS OF REPEATED FLUOROSCOPIES IN INFANTS

FRANZ BUSCHKE, M.D., AND H. M. PARKER
SEATTLE, WASH.

RECENTLY we became aware of the fact that apparently a number of pediatricians include a fluoroscopy in the monthly routine examinations of the infants in their care during the first and second years of life. Since we feel that such a procedure is charged with certain potential hazards, we welcome the opportunity of discussing this problem at your initiative in this group.

It is too often not realized that x-rays, in addition to being a useful diagnostic tool, accidentally and unfortunately represent at the same time a powerful drug. As Dr. Case once pointed out, x-ray diagnostic procedures are still considered by many as a kind of "glorified photography." Yet every exposure to x-rays actually delivers radiating energy to the body. The output of different diagnostic machines varies within very wide limits, depending upon the milliamperes and kilovolts used, the filtration, the distance between tube and body surface, the time of exposure, and the size of the exposed field. But even many specialized radiologists do not know the actual output per minute of their diagnostic machine.

Cowie and Scheele[1] have reported the result of a survey of radiation protection in forty-five hospitals located in twenty-four states scattered throughout the country, undertaken at the initiative of the National Cancer Institute. These hospitals were considered the type in which one might expect to find typical, if not slightly above average, equipment and practices of protection against high energy radiation. Although this survey was undertaken from the point of view of radiation protection for the personnel rather than for the patient, the inadequacy of protection during diagnostic procedures in a large number, even of these special radiologic units, shows the lack of appreciation of the amount of irradiation inadvertently delivered. It only goes to show that we can hardly expect a greater appreciation of these potential dangers where equipment used in office practice by physicians not specializing in radiology is concerned.

It is true that most of the machines today deliver a quality and quantity of radiation which, within reasonable limits of diagnostic exposure, will not cause any demonstrable gross damage. But what we have in mind are not so much the gross accidents but those potential dangers which are much more difficult to demonstrate. For the majority of diagnostic procedures used in general practice, the lack of

From the Tumor Institute of the Swedish Hospital.
Read before the North Pacific Pediatric Society, Seattle, Jan. 31, 1942.

appreciation of these potential hazards is regrettable but probably not a cause of major concern because these procedures in adults and older children are usually limited to fairly small portions of the body. If the small body of an infant is exposed to the same kind of radiation, a comparatively much larger volume of body is irradiated. This risk is naturally increased if such fluoroscopies are done repeatedly in infants at fairly short intervals. For this reason it seems necessary to give even more attention to details of the fluoroscopic procedure with infants in order to eliminate or minimize the possible detrimental effects.

We will meet, and as a matter of fact have repeatedly met, the objection that never has any damage been observed by those who have used this procedure throughout many years. But as we have already pointed out, the possible effects of doses under consideration here are much more difficult to demonstrate and, it is true, by their very nature can be anticipated only by implications from our general knowledge of radiation biology and from comparison of the doses delivered with those used for other therapeutic purposes. If we wait until damage is proved beyond the doubt of the unbeliever, irreparable harm may have been done.

Before entering into a discussion of these possible effects, we must determine the actual amount of radiation delivered during such fluoroscopies in order to substantiate our opinions as to their hazards. We have therefore investigated seven machines used in offices of reputable pediatricians selected at random. Not all of them do routine or even regular repeated fluoroscopies. Since, however, none of them knew the output of their machine, it is merely accidental whether those with higher outputs are actually used for repeated exposures. Table I represents a survey of this analysis, and though it is only a small and arbitrary selection, we believe that it permits us to draw some definite conclusions.

One of the machines, E, delivered at the supposed operation of 5 Ma., 35 r. per minute. The physician in charge, however, reported that the amperage is inconstant and that the amperes would change up to 40 Ma. without change of the controls. In such a case an amount of about 200 r. might be delivered to the infant's body in one minute. Wintz[2] considers 170 r. applied to the adult's ovary as sufficient to cause a temporary amenorrhea, and the dose necessary for a permanent sterilization of the adult's ovary varies around 300 r. (Martius[3]). Schinz and Slotopolski[4] caused a complete depopulation of a rabbit's testicle with only 60 r. The dose necessary for a temporary sterilization in man is considered around 200 to 300 r. (Schinz, Wintz), and we have the histologic proof of a complete atrophy without signs of restitution in a human testicle following the exposure to 600 r. (Schinz and Slotopolski). From an interpretation of available data it seems that the retardation of bone growths can be expected with doses of about 150 r. in infants and about 300 r. in small children (Ellinger[5]). In animals a marked retardation of growth was observed following doses below the epilation dose

TABLE I

X-RAY OUTPUT OF SEVEN MACHINES USED FOR FLUOROSCOPIES IN INFANTS

EQUIPMENT	NOMINAL CURRENT (MA.)	AVERAGE DOSE RATE ON SKIN (R. PER MIN.)	AVERAGE DOSE RATE 5.5 CM. DEEP (R. PER MIN.)	NOTES
A	5	6.0	1.2	
B	No milliammeter	6.3	1.9	Output variable
C	5	16.0	Not measured	Output so variable that screen brilliancy changed
D	3	28.0	4.0	
E	5	35.0	Not measured	Tube current varied freely from zero to 40 Ma.; output dangerously erratic
F	5	37.5	3.8	
G				
Operator 1	3	23.0	4.0	Two technicians used different technique on same machine
Operator 2	5	38.0	7.0	

The dosage measurements were made in a "presswood phantom" approximately the size and shape of an infant. By this method, the dosage figures obtained are the same as if an infant were actually used for the measurements. The body of the presswood infant was 11 cm. thick (anteroposteriorly) so that the dose 5.5 cm. below the skin represents the dose in the central regions of the infant body.

In all cases the dose rate was measured with a small field of irradiation (100 cm.^{2}) and again with a large field (350 cm.^{2}). The simplified table gives the average of these for each machine. On the skin, the large-field dose is approximately 20 per cent greater than the small-field dose. Within the infant body the difference is even greater.

The percentage depth dose at 5.5 cm. ranges from 10 per cent for F to 30 per cent for B. The main factors in this variation are the distance of the x-ray tube below the fluoroscopy table, the effective filtration of the beam, and the voltage applied to the tube. The exit dose was found to vary from 0.3 to 1.6 r. per minute, while the percentage exit dose covered the wide range of from 1 to 7 per cent. From the standpoint of minimum radiation damage, it is evident that optimum conditions require: (1) large distance between tube and table; (2) screen as close to body as possible; (3) voltage and filtration chosen so that incident radiation is as penetrating as possible, consistent with good fluoroscopic differentiation; and (4) tube current the minimum for good screen visibility.

If we may generalize from the small number of machines studied, it would appear that equipment especially designed for pediatric offices ignores the important factor of tube-table distance, using twelve or thirteen inches instead of eighteen to twenty-two inches of larger machines, while ordinary radiographic equipment, used permanently or temporarily for pediatric fluoroscopy, is likely to be operated at tube current well in excess of the necessary value. We made no investigation of the voltage and filtration, although this might well be discussed in view of the incidental observation that machines A, C, and D were virtually identical except for age, whereas the outputs at the same tube current were 6, 16, and 43 r. per minute, respectively. At the voltages involved in fluoroscopy the thickness and composition of the tabletop and the choice of a mattress are prime factors in regulating the radiation output.

(Fösterling quoted by Flaskamp[6]) which in human infants would mean below 300 to 400 r. Naturally these data cannot be applied to our problem without reservation, since details of technique, quality of radiation, etc., have to be taken into consideration. But they bring the dose which might possibly be applied during fluoroscopy with a machine such as the one under consideration so close to the danger zone as to justify serious concern. Although the use of such a machine today might be compared

with surgery without asepsis, probably quite a number of such machines is still in use and their potential danger should be emphasized.

In another place under the direction of one of the best radiologists we found that the output differed with the operator (machine G). While the physician assumed that he was always fluoroscoping infants with 3 Ma., we found accidentally that one of the technicians when he happened to be at the control would give him 5 Ma., increasing unnecessarily the output from 23 to 38 r. This example again emphasizes that even in the best places there is not sufficient appreciation of the potential hazards, and there is a lack of attention to details with the purpose of minimizing them.

Surveying the outputs of other machines as shown in Table I we find a variation between 6 and 38 r. delivered to the posterior surface of the infant's body. For the purpose of comparison we may mention that the doses given therapeutically for inflammatory conditions, such as a mastoiditis or a furuncle, or for a thymic enlargement are around 50 to 75 to 100 r. Although there is a considerable decrease in dose while the radiation passes the infant's body (due to the soft character of this type of radiation), it seems fair to base our discussion on the lower surface dose since the most endangered organs, ovaries, testicles, spine, and extremities in small infants are quite close to the tabletop. It seems fair for this discussion to conclude from our table an average dose of 25 r. per minute. If the average rapid fluoroscopy by an experienced and well-adapted examiner takes twenty seconds, about 8.3 r. will be delivered at this rate or 100 r. during the first year of life. Actually we know from experience that some of the fluoroscopies last considerably longer.

What then are the hazards we might anticipate for doses within this range?

Four main types of radiation damage must be considered: those to the skin, the hemopoietic system, the epiphyses of growing bone, and the gonads.

The doses here under consideration are too small to anticipate any damage to the skin and to the epiphyses, particularly since they are not additive over a longer period. There is a marked recovery from each dose, if the total dose is distributed over any length of time. Consequently there is a considerable difference as to whether the dose of 100 r. is applied at once or in twelve single doses with monthly intervals. The same is probably true for the effect on the hemopoietic system. In this regard, however, one should consider the fact that the type of fluoroscopic examination under consideration here is actually comparable to a total body irradiation. If this procedure is applied in adults for therapeutic purposes (as it occasionally is in certain stages of leucemias, Hodgkin's or other generalized diseases) the dose delivered to the entire or almost the entire body varies around 5 to 15 to 30 r. With such doses in adults a very marked reduction of the white and occasionally the red count might be observed, and the procedure therefore has to be applied

with the utmost caution. We have seen one case, a leucemic patient, in whom a total body irradiation of 10 r. was applied three times in ten days. This treatment was followed by an uncontrollable and fatal drop in the white count. Granted that probably the normal hemopoietic system of the infant will be more resistant than the diseased one, still the dose delivered to the entire body or large portions of it during such a fluoroscopy, as you can see from Table I, may come close to a potentially harmful dose even if it cannot be demonstrated by clinical methods at our disposal today. We also know that x-rays have an influence on the cell respiration and on the electrolytic metabolism of the cell, and thus they probably have other pharmacologic effects which cannot yet be demonstrated. Although there exists a vast amount of experimental work with regard to the physical, chemical, and physiologic-chemical changes produced by x-rays, no uniform conclusions can be drawn. But even if these effects are not yet uniformly interpreted, they should prompt us at least to consider the possibility of some metabolic disturbances if radiation is poured throughout the body.

The effect of radiation on the gonads is of two types. If a sufficient amount of irradiation is delivered, this will cause a complete and either temporary or permanent sterilization. The doses here under consideration (with the exception of those due to definite technical errors) are below this level.

Doses below this sterilizing level, however, are known which do not cause a destruction of the germ cells but do cause changes in the germ plasm; this means changes in the chromosomes and genes which are responsible for the transmission of inheritable characteristics throughout the generations to come. The doses in question here are well within the range in which such damage might be expected. Doses causing an increase in the normal mutation rate are completely additive in effects; this means the effect with regard to the number of induced mutations is the same whether a certain dose is applied at once or in intervals of days, hours, months, or years. It has been shown that the doses are even additive in succeeding generations. Duration and frequency of exposures do not influence the reaction. The result of more recent exposures simply add to the previous exposures. The number of mutations induced is in direct proportion to the total dose delivered to the gonads and is independent of the quality of radiation. The importance of these facts in their bearing on the problem under consideration is quite evident. Muller[7] has computed that if irradiation causes an increase in the mutation frequency of man similar to that in Drosophila, then it would take an average treatment of only about 30 or 40 r. per individual to make the rate at which hereditary weaknesses and lethals are produced double the natural rate. Since this effect is actually accumulated over an indefinitely long period of time, it is well possible that if germ cells received only a little secondary radiation but repeatedly at widely

separated intervals, even in successive generations, the final effect would be a production of mutations as great as though the whole treatment had been given at once (Muller[7]).

The clinical manifestations of such effects which we can anticipate are of three types.

First, a general decrease of fertility in the generations to come. This is due to two different kinds of damage to the germ plasm: to chromosomal changes and to lethal gene mutations. The chromosomal changes consist of pathologic disturbances of the normal chromosome divisions. From the point of view here under discussion these changes may appear more important than the gene mutations because the chromosomal changes may cause a marked infertility even in the first generation offspring of the irradiated individual and therefore may appear somewhat closer to the general way of thought of the clinician. Lethal gene mutations consist of sudden changes of the single unit of heredity (the gene) in such a way that this particular change is incompatible with the life of its carrier. The lethal gene kills the spermovium, or the embryo, in early stages. It is now assumed that quite a number of sterile couples carry such lethal genes. Since most mutations are recessive (i.e., able to produce their characteristic effect only when an individual has received the same kind of mutated gene from both his parents) they will be lethal only when both parents are carriers. This would explain that in some of these couples either partner may be fertile if mated to another partner who is not a carrier of this gene. This type of damage will clinically manifest itself only in the third and following generations of the irradiated individual. From the point of view of quantity, this type of damage is probably the most important one since at least 80 per cent of the x-ray-induced mutations (as the spontaneous mutations) are completely lethal in their effect.

Second, an increase in the number of those persons in the general population who are afflicted with inheritable disease. This effect is due to the increased production of so-called sublethal genes and of genes which cause marked morphologic or physiologic disturbances not severe enough, however, to cause the death of the individual in the embryologic stage. They may either cause death during early life, such as from ichthyosis congenita, amaurotic idiocy, xeroderma pigmentosum with the development of skin cancers, or they may cause definite disease entities which are still compatible with life, such as diabetes, susceptibility to tuberculosis, cleft palate, certain diseases of the central nervous system, etc. The borderline between the sublethal genes and those causing marked minus variations in a viable organism is not sharp and depends upon many external circumstances. We know for instance a race of dogs with a marked inheritable tendency for the development of cleft palate causing early deaths of the puppies because of the impossibility of nursing whereas the same defect in human beings today is compatible with life following surgical intervention.

Third, only slight variations in physiologic or morphologic behavior. This group probably represents the most common but the least easily recognizable group. There are probably many physiologic changes that remain undetected because they have no outer morphologic expression at all. After all, it is partly a matter of one's philosophy of life whether he considers certain deteriorations already as pathologic. This thought was best expressed by Colwell and Ross[8] in their discussion of these problems:

"We believe that 'intelligence tests' on certain rodents have been carried out, but the normal intelligence of rabbits and guinea pigs is not usually regarded as high. And in considering the matter now under discussion, mental changes are of at least as much importance as anatomical variations. Equally, as we have indicated before, it does not help the case very much to take a collection of birth statistics and report that when the mothers had been subjected to (preconception) ovarian irradiation 'the pregnancies and the offspring were quite normal.' What may be quite 'normal' mentality and capacity in one social grade may be a marked degeneration in another. Apart from gross mental deficiencies such as idiocy or semi-idiocy, simple 'weakening' of intellect or of business capacity in the children will be much more obvious when the parents belong to the professional classes or even to the numerous class of skilled work people than when they follow some unskilled occupation. In cases like these relative values are of the highest importance.

"Parents in general wish to do the best for their children. Is subjecting the mother's ovary to radiation doing the best? The question of causing gross anatomical lesions does not enter into the discussion. If it did, there would be no discussion at all."

The fact that these slight mutations show only very indefinite manifestations does not make them less objectionable but more so since they would be harder to recognize and deal with and will lead to a general deterioration of the race. Since many of these properties probably are those of somewhat reduced efficiency of the central nervous system, it is partly a matter of how much importance one attributes to the efficiency of the brain function in general and whether he considers these variations very important or not.

How real are these dangers to the germ plasm?

To most clinicians all arguments based on genetic considerations appear somewhat as fairy tales. This is due to the fact that definite conclusions in the field of genetics can be reached only by statistical evaluations of a vast number of observations throughout many generations. Obviously therefore conclusions in regard to human pathology can be reached only in analogy to those obtained by animal and plant experiments. And the clinician has a certain instinctive hesitation to accept conclusions reached in this way on the fruit fly as applicable to the

human race. The uniformity, however, of the Mendelian laws throughout the animal and plant kingdoms must be considered today as proved beyond any possible doubt. While details naturally differ, the fundamental conclusions reached on the basis of an overwhelming experimental evidence in animals and plants can safely be applied to the human race. No field of radiation biology rests on so safe an experimental basis as radiation genetics. While it is of course impossible to give even a superficial review of the experimental evidence on which our conclusions are based, we refer those who wish to convince themselves of the soundness of these inescapable conclusions to some of the elaborate reviews by competent radiation geneticists such as Muller,[7] Timoféeff-Ressovsky,[9] Hanson,[10] Oliver.[11]

On the basis of the experimental evidence which has shown that irradiation of the gonads causes a marked increase in the normal mutation rate in proportion to the dose, geneticists have warned again and again and for many years against the danger of indiscriminate exposure of the gonads to x-radiation. In a discussion of this problem in 1938, which was mainly concerned with the question of such danger from the point of view of radiation therapy, we considered this danger as exaggerated by the geneticists. We felt that, since most of these mutations are recessive in character, the occasional irradiation of the gonads would not increase the number of such recessive genes in the population at large sufficiently to increase appreciably the clinical manifestation of these genes which occurs only if both parents of an individual are carriers of these recessive characters. *This danger, however, naturally increases considerably if the gonads in a large proportion of the population are routinely exposed to irradiation.* In this way the number of mutations in the general population would considerably increase, and consequently the chances of the meeting of two recessive characters may become great enough to have practical consequences. If this routine is followed we might embark upon a gigantic experiment. The blueprint of the results which we might anticipate are in our possession in the form of the large scale experiments on Drosophila and other organisms. We might then face the paradoxical situation that while modern medicine tries by different means to eliminate defect variations, the same medicine itself produces these mutations for the generations to come on a scale much larger than nature ever attempted to do. Whether in view of the present world conditions such a change of the human race or its decreased fertility is objectionable is of course a matter of one's personal philosophy of life. The chances that the race becomes deteriorated are certainly greater than those that it will improve, because most of those mutations which are not lethal are to some extent detrimental to life, although occasional improvements were found experimentally. When changes are induced in a random fashion in a highly organized system, it should then be expected that only a very few of these random changes would happen not to be harmful (Muller).

From time to time we find in the radiologic literature reports on the offspring of mothers whose ovaries have been subjected to irradiation, and pictures are shown of apparently healthy babies born after such procedures. Since, as emphasized, most of these mutations are recessive, we will not expect any damages before the third or following generations. The decrease in fertility cannot be denied by pointing at and photographing those babies who are born. The appearance of a baby does not say anything about the further development of this child. Since we do not expect mainly gross variations but more a general but immeasurable deterioration in those who will be born, the normal appearance of a baby and even of an adult is meaningless.

CONCLUSIONS

The purpose of this discussion is not to discourage your fluoroscopies when you consider them as *clinically indicated.* We only mean to make you appreciate that fluoroscopy actually delivers radiation energy in doses which may cause certain detrimental effects and to use all possible precautions in order to minimize the risks. These safeguards we may summarize as follows:

1. The output in roentgens per minute during fluoroscopy should be known to the examiner and should be kept in mind. This means that diagnostic machines should be calibrated and should be checked at regular intervals, at least every six months.

2. The actual output should be kept as low as is compatible with the efficient diagnostic procedure. We have convinced ourselves that the screen picture with those machines in this series which gave the lowest output (6 r. per minute) are sufficient for most diagnostic purposes in fluoroscoping the small body of an infant. The milliamperes and kilovolts then should be adapted to what is really necessary. In order to keep the output as low as possible, a good adaptation of the examining physician and a good screen are prerequisites.

3. The exposure time should be kept as short as possible. No discussion of the fluoroscopic findings is permitted as long as the shutter is open. This naturally means that an explanation of the screen picture to the baby's mother during fluoroscopy is not permitted.

4. The shutter of the fluoroscope should be open only as far as is absolutely necessary for the diagnostic purpose. If ever possible, any exposure of the abdomen and of the gonads should be avoided altogether.

5. In cases in which it is doubtful as to whether the fluoroscopic examination will lead to a conclusion, it may be better to have a film exposure done with an efficient machine. This is true, for instance, for the location of foreign bodies. A rough investigation has shown us that an average film exposure of this type delivers only about $\frac{1}{10}$ r. This picture can be studied quietly. If then fluoroscopic examination becomes necessary for further localization, the field can be limited and the time

of exposure can be shorter because one approaches the problem with a more definite question in mind. We do not believe that fluoroscopic examinations give any adequate information as to the condition of the epiphyseal lines. Minor disturbances will escape fluoroscopy and need first-class film exposures. Once they are intense enough to be visible on the screen they will not need "routine" examinations.

6. Machines which cannot be calibrated adequately and are unreliable in their output, such as the one described by us as E, should be completely discarded as unsuitable.

REFERENCES

1. Cowie, D. B., and Scheele, L. A.: J. Nat. Cancer Inst. **1**: 767, 1941.
2. Wintz, H.: Strahlentherapie **37**: 407, 1930.
3. Martius, H.: Strahlentherapie **42**: 160, 1931.
4. Schinz, H. R., and Slotopolski, B.: Ergebn. d. med. Strahlenforsch. **1**: 443, 1925.
5. Ellinger, F.: Die biologischen Grundlagen der Strahlenbehandlung, Berlin, 1935, Urban & Schwarzenberg.
6. Fösterling: Quoted by Flaskamp, W.: Roentgenschaeden, Berlin, 1930, Urban & Schwarzenberg.
7. Muller, H. J.: The Science of Radiology, Springfield, 1933, p. 305.
8. Colwell, H. A., and Russ, S.: X-ray and Radium Injuries, Prevention and Treatment, London, 1934, Oxford University Press.
9. Timoféeff-Ressovsky, N. W.: Ergebn. d. med. Strahlenforsch. **5**: 129, 1931.
10. Hanson, F. B.: Physiol. Rev. **13**: 466, 1933.
11. Oliver, C. P.: Quart. Rev. Biol. **9**: 381, 1934.

Critical Review

FOOD CONTAMINATIONS AND POISONS

PART II

(Concluded)

GEORGE M. LYON, M.D.
HUNTINGTON, W. VA.

OTHER FORMS OF FOOD INTOXICATION

POISONS NATURALLY PRESENT.—Many plants contain poisonous substances. Those of an alkaloidal nature are probably the most important and best known. Although it is desirable to indicate the relationship of such poisons to our general subject, time does not permit a careful discussion of this fairly well-understood class of food poisons. Of the alkaloidal poisons, there are three besides those of ergotism and lathyrism, described later, which merit consideration.

Coniine, found in all parts of common or spotted "poison" hemlock *(Conium maculatum),* has produced deaths when the root has been eaten mistakenly for horse-radish or parsnips or the leaves for parsley, or from mixing hemlock seeds with anise seeds.

Aconitine, from various members of the species Aconitum, has been responsible for accidental poisonings when the root itself or a decoction of it was taken in mistake for some other root, usually horse-radish.

Colchicine, from the meadow saffron *(Colchicum autumnale),* has caused accidental poisoning when the leaves have been eaten for salad and also when the seeds have been eaten by children.

Webster stated that deaths from the ingestion of *cyanophoric glucosides* in various plants have occurred. *Phaseolus lunatus,* commonly known as Rangoon beans or Moon beans, contains such a substance. Within the intestinal tract hydrocyanic acid is liberated from these beans. It is reported that these beans may contain from 8 to 56 mg. of hydrocyanic acid per 100 Gm. of beans. In millet, flax seeds, and some species of vetch, similar cyanogenous glucosides are found. Amygdaloside (amygdalin) is found in the leaves, bark, flowers, and fruit of cherry and laurel, plants of the genera Prunus, Cerasus, Sorbus and Spiraea, and in the seeds of cherry, plum, peach, apricot, apple, and pear. It is present in bitter almonds to about 3 per cent. "Oil of bitter almonds" has caused poisoning and should never be used for flavoring. "Synthetic oil of bitter almonds" (benzaldehyde with no hydrocyanic acid) is not dangerous when used as a flavoring.

Mushroom poisoning (mycetismus) results from eating *Amanita phalloides, Amanita muscaria,* or other related poisonous fungi. There are at least eighty species of poisonous fungi. Ford has described five forms of mycetismus (gastrointestinalis, choleriformis, nervosus, sanguinareus, and cerebralis).

Amanita phalloides is probably the most important because it causes the highly fatal mycetismus choleriformis which is characterized by a mortality rate of 50 per cent or more. In this intoxication first there

are gastrointestinal symptoms followed later by loss of strength, paroxysms of pain, anuria, delirium, coma, and death. Convulsions may occur.

Amanita muscaria, as well as other fungi containing muscarin, give rise to mycetismus nervosus, a much less fatal form, and the only one for which an effective antidote is available (atropine). Sweating and salivation are the characteristic symptoms. Early there may be gastrointestinal symptoms and later, delirium, hallucinations, convulsions, and coma. In the milder attacks there may be simply a transient vomiting and diarrhea or profuse sweating and salivation.

Mycetismus resulting from other less poisonous fungi are characterized in one group (a) (gastrointestinalis) by an extreme nausea and diarrhea, transient in character and with a very low mortality rate, in another group (b) (sanguinareus) in which gastrointestinal symptoms are followed by hemoglobinuria and in which a low mortality rate prevails, and by still another group (c) (cerebralis) in which transient cerebral symptoms, such as excitement and hallucinations, are the main features.

Damon has said. "Unfortunately, there are no simple tests by which the layman may distinguish the poisonous from the harmless species. It cannot be too strongly emphasized that such commonly applied tests as peeling the top or pileus or cooking with a silver spoon are worthless as indicating the innocuous or poisonous varieties, nor can any more confidence be placed in the taste of the fungi as some of the most poisonous mushrooms have an agreeable or even delicious flavor."

The most common form of mushroom poisoning results from eating *Amanita phalloides.* Children are noticeably more susceptible than adults.

The clinical picture of mushroom poisoning, even when the gastrointestinal symptoms predominate, is quite unlike that of the acute food poisoning due to salmonella and staphylococci. (In one instance a botulinus intoxication was traced to canned mushrooms. It was at first assumed that a toxic fungus had been packed in place of the harmless mushrooms.)

Fish poisoning (ichthyotoxismus) results from eating fish that by nature contain poisonous substances within their bodies. In some, such as the Tetrodontidae (puffers) and the Diodontidae (porcupine fish), the poison is found only in the head, liver, or ovaries, while in others, such as some of the Clupeidae (herring family), particularly *Clupea thrissa* and *Clupea venonosa,* and certain of the Scari (parrot fish), the poison is found distributed throughout the body.

The term fugu poisoning is applied to the form of ichthyotoxismus resulting from eating "puffers" and other fish containing fugin, a poisonous substance which resists prolonged boiling and behaves like a basic substance with alkaloidal properties. The poison is present in these fish throughout the year and not just at spawning season, as some of the other poisons are in other fish. The acute symptoms are of the nervous and digestive systems, headache, restlessness, salivation, vomiting, paralysis, cyanosis, dilatation of the pupils, and death from dyspnea. The toxin has a paralytic action on nerve fibers. It is a highly fatal form of food poisoning. This condition is encountered in Japan, the East Indies, and other tropical areas where these fish live.

Ingestion of the poisonous members of the family Clupeidae results in a severe gastroenteritis. Fatalities are common. It has not been a simple matter quickly to differentiate clinically between ichthyotoxismus

due to physiologic poisons present in the fish and that form of food poisoning resulting from bacterial contamination of the dead fish, because fish readily become infected, or contaminated, with organisms which may produce gastroenteritis. Many pathogenic and saprophytic forms have been suspected and partially incriminated. In temperate climates much of the food poisoning from fish results from microbic growth in the dead fish. Among these the staphylococci are the most important in North America. Less frequently the salmonella are responsible. Fish may harbor any of the pathogenic bacteria (or viruses) available in their watery environment, particularly the typhoid and paratyphoid organisms. The staphylococci gain access through handling in preparation of the fish for eating.

Certain of the fish of the sturgeon family (Acipenseridae), the pike family (Esocidae) and "barbel" (species Barbus) may have poisonous substances within their bodies during the spawning season but not at other times. The poison is closely related to the reproductive organs rather than widely distributed throughout the bodies.

Shellfish poisoning will be discussed later. As far as is known now, the shellfish contain poisons not constantly present as "physiologic poisons": most so-called shellfish poisoning in the United States results from (1) staphylococci contamination or (2) allergic sensitivity. Milk and fish are not incompatible foods, as tradition relates.

Ample references to the forms of poisonings just referred to are to be found in texts and in the literature. Not so well known, however, is the fact that some birds, notably some owls, and even hawks, regularly contain deadly poisons. Dr. Thurman Rice* has graphically described an experience in which he studied epidemiologically an outbreak of so-called food poisoning in which there were, besides some deaths, some extremely ill persons as a result of the shooting and eating of the "big chick," as the screech owl is known to some of the foreign-born residents of northern Indiana.

Poisons Not Naturally Present.—

Metallic and Chemical Poisons: Pure food laws are established to protect us from many evils. Most commercial food packers and distributors accept their responsibility and guarantee their products to be free from harmful substances. In spite of this, however, at times, through accident, carelessness, or ignorance, foods may be contaminated at the source of production. Most contaminations of a serious nature arise after the product has left the hands of the original producer.

Through modern technical guidance the food industry has reached such a high peak of efficiency and perfection that poisonous chemical compounds rarely get into food at the source of production. Nevertheless accidents do occur. An occasional, although infrequent, occurrence is for some company to experiment with certain chemical compounds at the risk of public welfare. Most food packers and processors, however, appear to face their responsibilities in this respect with genuine conscientiousness.

Foods may be contaminated with metallic or other poisons in a variety of ways.

It may be helpful from the standpoint of epidemiologic approach to consider, in a topical outline, examples of the various ways in which food may be contaminated by chemical poisons.

*Personal communication.

Contaminated at the Source
- Added purposefully (formaldehyde, copper sulfate)
- Insecticide spray (lead arsenate on fruit and vegetables)

In Distribution
- Contaminated after packaging
  - Container itself poisonous (some plastics)
  - Container previously contained poison (vinegar in white lead barrel)
- Container reacts with contents
  - Physical solution (lead)
  - Chemical reaction (cadmium from lemonade in "aluminum" pitcher)
- Container penetrated
  - Cellophane or paper wrappers penetrated (fumigant sprays)

In Preparation
- Added in preparation (Easter egg dyes)
- Contaminated in cooking (lead fumes in bread)
- Accidental
  - Poisonous ingredients (vinegar from contaminated peelings of apples)
  - Mistaken additions (insecticide for flour)

Miscellaneous
- Silverware cleaned with polish containing cyanide
- Water containing fluorine (mottled teeth)
- Stock fed on contaminated vegetables and fruit (lead arsenate)
- Vegetation grown on contaminated soil
  - Cattle and turkeys in the Northwest (lead arsenate)
  - Monstrosities in cattle (seleniferous soils)

Harmful agents have been added at the source of production as a preservative to improve color, etc. (formaldehyde, copper sulfate).

Fruits and vegetables sprayed with insecticide may be highly contaminated (lead and arsenic in fruits and green vegetables).

Because some lacquers used in lining containers for food products have been poisonous, this problem is receiving much attention at the moment by appropriate agencies. Likewise, plastics which may be used as food containers present a similar problem. Some are definitely unsuitable for use.

Some containers are poisonous because they have previously contained poisonous compounds (vinegar from a white lead barrel). Arsenic poisoning occurred from olives that had been placed in secondhand barrels which had previously contained lead arsenate. Vinegar containing 0.035 Gm. of arsenic trioxide per pint has been obtained from a barrel previously used for white lead.

Excessive contamination with lead has followed the use of lead-lined containers, evaporators, or other equipment as a result of physical solution. This was more common in the days when pewter contained lead.

Packaged products may be put into containers which permit fumigant sprays to penetrate (cyanide for packaged raisins).

Easter egg dyes containing cadmium sulfide, zinc sulfide, barium sulfate, and varying amounts of lead have in times past been found on the market.

Bread contained lead when it was baked in an oven heated by a fire made from plates of a battery. Lead poisoning resulted.

A very important form of food contamination results from carelessness, criminal carelessness, in the pantry or kitchen. This is typified by the use of a fluoride insecticide in the place of flour in the making of griddle cakes.

Silverware has been cleaned with polish containing cyanide, and poisoning has resulted therefrom.

Vinegar made from apple peelings contaminated with lead arsenate has produced poisoning.

Plants grown on soil laden with harmful chemicals have been highly toxic (cattle and turkeys in orchards of the Northwest). The seleniferous soils of North Dakota produce vegetation which is highly toxic to live stock (deaths, selenium monstrosities).

In spite of the strict ban now placed on most of the so-called food preservatives, not more than six years ago cream preserved with formaldehyde was found in interstate commerce and was the subject of federal seizure.

A committee from the American Public Health Association,[73] as a matter of broad policy, has urged that the addition to food of chemical preservatives, excluding of course, such time-honored substances as sugar, salt, and vinegar, be discouraged. They point out that with processes of pasteurization, heat sterilization, freezing, and dehydration available for the preservation of most classes of food, there is generally no need for the adulteration of the produce by the addition of foreign substances.

Members of the same committee,[73] in commenting on practices which have been known in which chemical contaminants were added to food, resulting in illness of consumers, pointed out that it should not be construed as a general criticism of prevailing methods of food production. They said there was no cause for alarm regarding the purity of our food supply, quite the contrary, and that the cases cited were exceptional and unusual. It was their belief that if it were possible to know of every case of physical distress due to contaminated food, it might be found that those caused by the accidental inclusion of poisonous chemical compounds in the home far outnumbered those due to the type of contamination already discussed, and that there are sufficient records of authentic cases of household or "pantry" contamination to support this conjecture.

In a southern state, flour heavily contaminated with calcium fluoride was used in preparing a gravy, the consumption of which resulted in the death of two persons. An identical type of contamination of corn meal caused serious illness in a midwestern labor camp. In a New England city poisoning in a family was traced to the use of flour containing dangerous amounts of an arsenical insecticide. The inadvertent use of lead acetate in pie meringue was the cause of illness in a Texas community. A Christmas fruit cake prepared in Virginia from flour mixed with calcium arsenate has been reported. In all of these, contamination took place on the premises where the food was consumed. There have undoubtedly been countless such instances not reported and of which there is no authentic record.

Such cases are probably beyond legal control. Their prevention appears to lie in educational measures aimed at the safe use and storage of insecticides, raticides, and other poisons in such a manner that they cannot come in contact with food, and, in an effective way upon the emphasis of the need of plain marking or packaging such products in such a way as to show their identity and their poisonous character. Conspicuously colored products themselves might serve to distinguish them as such.

The Federal Food and Drug Administration[73] investigated an outbreak of food poisoning in a family, three members of which had eaten uncooked raisins. The evidence pointed fairly clearly to the raisins as the vehicular food. Chemical analysis of the remaining raisins re-

vealed that they contained 3,000 parts per million of hydrocyanic acid. The packaged raisins, after being held in storage for a time due to emergency conditions arising from a long-drawn-out maritime strike, were exposed to a fumigation technique which has previously appeared to be satisfactory. Since not all packages were equally contaminated, it appeared that the explanation of the matter lay in the splattering of droplets from the atomizing nozzle. In this manner some of the packages were wet with the liquid hydrocyanic acid. A nationwide survey of dried raisins, under the Federal Food and Drug Act, resulted in the seizure of thirty-five lots of raisins, a total of 140 tons, containing enough cyanide to warrant seizure. It is pointed out that, previous to the affair, the dried fruit industry had largely abandoned the use of hydrocyanic acid as a food fumigant, and in its place was using less toxic agents such as ethylene oxide, ethylene dichloride, chlorpicrin, and ethyl formate. There is reason to believe that the use of cyanide has been definitely abandoned in the dried fruit industry. In commenting on this matter, members of a committee from the American Public Health Association pointed out the desirability of having fumigation processes carried out under a stringent system of control. As new compounds of unknown toxicity are introduced for such fumigation purposes, they should be viewed with suspicion and their adoption postponed until careful scientific study has proved them harmless.

Hanzlik,[72] in describing the "health hazards of chemo-enemies in contaminated foods," has called attention to an insidious danger not properly appreciated by most of us. He emphasized in particular the dangers of chronic intoxication from repeated ingestion of tiny amounts of heavy metals and pointed out that while the dramatic aspect and the potent effects which follow the use of, or the swallowing of, large doses of the heavy metals attracted appropriate attention, there was little concern generally for the slowly developing and continuing effects of the tiny quantities to which vast populations are exposed day in and day out. Exposure to these dangers results from the use of heavy metals in combating insect pests of fruits and vegetables. Lead and arsenic are particularly commonly used. As you know, the former is an accumulative poison and concentrates in the viscera and bones from which it is gradually and continuously released in accordance with the influences of various states which may exist within the body. Whether the lead comes from the storage depots or from fresh absorption, it makes little difference, for it is this continued streaming of lead through the body which eventually injures important bodily functions. The connection between the resulting injury and the causative contaminant is not generally recognized. As Hanzlik sensibly pointed out, chronic poisoning with such metals is really a disease and not a poisoning in the sense that laymen ordinarily see it. He has described symptoms of chronic poisoning observed in localities where insecticidal sprays are used as characterized by such symptoms of asthenia as loss of appetite, loss of weight, weakness, fatigue on exertion, anemia, constipation or other gastrointestinal disturbances, and, later, pains in the joints, and nerve paralysis. He suggests that in the presence of these symptoms and in the absence of other known causes one should suspect chronic poisoning and further that such symptoms are more common or more aggravated during spring seasons. Analysis of the excreta or the blood for lead may provide conclusive evidence. A recent clinical and pathologic study from the Mayo Clinic provides evidence of Hanzlik's prediction that chronic poisoning results in a baf-

fling and not well-recognized clinical picture. Ecker and Kernohan[74] reported clinical, chemical, and pathologic studies on chronic arsenic poisoning ("chemical encephalitis") in patients whose ages ranged from 4 months to 65 years. The outstanding symptoms were headache, physical and mental fatigue, usually with dizziness, restlessness, excitability, mental dullness, and manifestations of cerebral symptoms. Analysis of brains showed as much as 0.10 to 0.83 mg. of arsenic per gram of brain tissue, the same as is found in instances of acute arsenic poisoning.

According to Hanzlik,[72] while the eating of one apple a day with a given degree of contamination for weeks or months would be hazardous to health as far as lead content is concerned, three or four similarly contaminated apples daily would be required for the effects of arsenic. From the standpoint of chronic absorption, the hazard from lead is several times greater than that of arsenic. Analyses were made of contaminated cauliflower and contaminated cabbage obtained in the open market in the Southwest. The cabbage contained 0.02 to 0.45 gr. of arsenic and 0.09 to 1.24 gr. of lead per pound. As 1 to 2 gr. of arsenic may be toxic or fatal to an adult, 1 pound of this cabbage would have contained ¼ to ½ of a toxic or fatal dose. An ordinary serving of cole slaw of 4 ounces would contain 1/16 to ⅛ of the killing dose of arsenic. This would be in addition to the lead. When lead and arsenic act together, the effects are additive and the amount of contaminated food producing illness would be less than if either material were present alone. Children would be more liable to such injury since they would consume a larger amount of the poison per pound of body weight.

No matter how carefully one may wash the sprayed apples or vegetables, there remains a variable residue on the skin, around the stem, and in cracks, fissures, or other inaccessible parts. The less washing and mechanical removing, the more lead arsenate will remain on the skin. While dilute hydrochloric acid solutions are used to remove some of the spray residue, once the chemical enters the stomach, the hydrochloric acid of the stomach increases the solubility and absorption of the chemical within the alimentary canal. This is just as true of animals fed on scraps. Simply paring the apples or carelessly wiping them off before eating, or failing to consume the area around the stems does not, according to Hanzlik, remove the poison. It is certainly not safe to leave this to children. Several such apples eaten daily may produce acute poisoning.

Hanzlik[72] pointed out that the toxic effects of lead have been observed in domestic animals feeding on contaminated foods, pastures, and water supplies. When spraying is done carelessly, sources of food supplies for man and animals may become contaminated. Turkeys allowed to run in sprayed apple orchards are known to have developed lead poisoning. Horses feeding on grass grown between the sprayed trees have died in three or four years from accumulative poisoning. Drift carried to pastures during airplane spraying of adjoining ranches has resulted in repeated indemnities for acutely poisoned livestock. Hanzlik described one valley in the Pacific Northwest as having received as much as seven million pounds of lead arsenate annually for the past twenty years. Fifty thousand tons of the chemical have permanently contaminated the soil of this valley. This is not washed away by rains, as the soil retains most of it permanently by absorption. Just what possibilities of chronic absorption and poisoning are vested

in the constant consumption of vegetables for animal and man in that area make one shudder. Hanzlik pointed to such a possibility as a very, very serious public health problem.

Lead arsenate or other arsenicals are not suitably safe sprays for vegetables like string beans, kale, spinach, cauliflower, cabbage, Brussels sprouts, celery, or broccoli. As a rule such vegetables are eaten in their entirety.

Better means of removing spray residue are needed and should be employed by producers.

The skins and residue of sprayed fruit should not be fed to animals or used in making jelly, vinegar, cider, or other food products; nor should poultry or livestock be fed on parings and skins of commercially grown fruits, or the pods, husks, or tops of commercially grown vegetables.

Attempts to use fluorine and selenium as insecticides have been made, and both have been found to be unsafe, fluorine endangering the teeth and selenium providing monstrosities among domestic animals.

Poisons Occasionally Present.—Among other poisons occasionally present in that which may be taken as food are some of considerable practical importance. Of the more rare forms, some present unusual interest, largely because of academic significance.

Rosenau states that the milk of nursing women may contain aspirin, iodine, mercury (calomel), arsenius acid, potassium bromide, salicylic acid and salicylates, ether, bromides, antipyrine, opium, volatile oils, purgative salts, rhubarb, and a long list of other drugs. The flavor of cow's milk is affected by many foods upon which the cow may feed, such as turnips, garlic, ramp, mouldy hay and grain, damaged ensilage, fermented distillery waste, etc. Ensilage, when fed to cows, may cause a laxative effect to appear in the milk which may produce diarrhea in an infant.

Milk sickness is due to ingestion of the milk, milk products, or flesh of an animal having the disease "trembles." Although primarily a disease of animals, man may be secondarily affected. The picture is that of an intoxication rather than an infection. The rayless goldenrod and white snakeroot contain a toxic substance responsible for this form of poisoning. This form of poisoning was formerly quite common in Tennessee and in other southeastern states where the cattle fed on wild plants. It is told of how epidemics of this poisoning plagued the pioneers, forcing them to move to other places where the weeds did not grow so commonly. In cattle the disease is called trembles and in man, milk poisoning. The onset is usually sudden, as in food poisoning, and although there are nausea and vomiting, there is no acute gastroenteritis, and constipation may be stubborn. The tongue becomes greatly swollen, dark red in color and tremulous, the cheeks flushed, the lips red. There is little, if any, fever, and the scanty urine contains the toxic substance. Abdominal pain and muscular weakness may be present. The patient may become irritable, then comatose, and die, death occurring as in severe intoxication.

Among those *fish poisonous only at the spawning season*, the following have been cited: members of the sturgeon family, the pike, and barbel.

Of particular interest because it exemplifies the complexity of epidemiologic investigation in matters of food poisoning and because it may indicate the mechanism whereby other seafood may be poisonous at certain seasons of the year only because of its food at that time is

the fascinating work of Meyer and his collaborators in a study of the mussel poisonings along the coast of California.

Mussels and clams in some localities may, during certain seasons of the year (summer and early fall only) contain a powerful neurotoxic poison which causes death by respiratory paralysis.

Meyer, Sommer, and others[68-70] at the Hooper Foundation in California have done much to solve the mysteries associated with this curious form of poisoning.

A man ate eighteen mussels and died with respiratory paralysis three and one-half hours later.

A 2-year-old boy drank a small cup of broth with three mussels and died five and one-half hours later.

Since 1927, 243 instances of poisoning of this type have been reported on the West Coast, mostly in the area centered around the Golden Gate. Similar happenings have been reported in Japan, Germany, France, Scotland, and Norway.

Meyer and his co-workers[69] traced the poison to plankton and open sea water upon which the mussels fed. Then the poison was demonstrated in plankton residue. Later it was observed that toxicity determinations on mice paralleled the numbers of a particular dinoflagellate contained in the mussel. Clearly it was shown that relatively large numbers of the dinoflagellate of genus Gonyaulax contained demonstrable amounts of the neurotoxin, and this was accepted as the source of the poison.

Clams from the same areas were shown to contain the same poison, concentrated in the livers. It was also found similarly in the large sand crabs.

The neurotoxin was not destroyed by heating, so cooking did not provide safety. In action it had both a central and a peripheral neurotoxic effect.

Three types of symptoms have been described:

1. Gastroenteritis with nausea, vomiting, and diarrhea was observed in a form which is usually not fatal.

2. Nervous symptoms characterized by diffuse erythema, urticaria, angina, and dyspnea were more common. Recovery usually occurred in a few days.

3. Paralytic form in which the symptoms simulated curare poisoning with respiratory paralysis as the outstanding feature was the most dangerous form. It was nearly always fatal.

Plankton, besides being associated with mussel poisoning in salt water mollusks, has also been associated with waterbloom poisoning in fresh water lakes. Cattle have been poisoned by drinking from fresh water lakes or ponds in which there was a profuse growth of plankton. Animals are said to have died within an hour after drinking from fresh water lakes containing such plankton growth. Whether it is due to the plankton or to the products of its decay is not known. So far, no associated dinoflagellates have been incriminated. The poison has been demonstrated in the water of such lakes but its nature has not been identified.

The demonstration of this poison in the water of these lakes is of interest to those working with the problem of stream pollution as it relates to drinking water. Some investigators have felt that the algae and other plant life which grows so profusely in our modernly dammed up rivers may not only be responsible for changes in taste but even

may be of importance in the production of acute gastroenteritis when such water is drunk. Tisdale, who spent many years studying stream pollution in the Ohio River, described an outbreak of gastroenteritis in Charleston, W. Va., during the drought of 1930, which, in all likelihood, had some relationship to the great overgrowth of such plant matter in the stagnant Elk River pool from which a part of the local water had to be obtained. On more than one occasion during periods of drought widespread occurrence of gastroenteritis has appeared to be associated with water of poor potability, obtained from streams having a negligible rate of flow, and with a heavy algae formation with the sluggish stream. It would not be surprising if there may not be derived therefrom some poisonous factor not totally unlike that responsible for "waterbloom poisoning." We have much yet to learn of marine toxicology and its relation to gastroenteritis, no matter whether it be in salt or fresh water.

Lathyrism results from the ingestion of certain varieties of peas *(Lathyrus sativus, Lathyrus cicera, Lathyrus clymenum)*. It is endemic and epidemic among men and animals of certain parts of the world, notably India and the Mediterranean areas. It appears to be due to a volatile alkaloidal principle of the seed, lathyrin. Present knowledge indicates that the peas are poisonous only when cultivated with a weed "akta" *(Vicia sativa var. angustifolia)*. The disease affects mostly the poor and fatigued. Cramps in the legs, weakness, and lumbar pains appear. The calves are affected first, then the thighs. The neurologic symptoms are interesting, remotely suggesting "jake leg" poisoning of our own prohibition days.

Potato poisoning results from the ingestion of sprouted potatoes containing a glucosidal alkaloid, solanin. While it is also found in several species of Solanum (black nightshade, bittersweet, potato), in the potato it is found in greater concentration in or near the peel. Immature, sprouting or diseased potatoes may yield a relatively high solanin content. This is particularly true of the sprouts themselves. This may have given rise to the fear of new potatoes for small children. The symptoms are vomiting, diarrhea, colicky pains, headache, depression, pain in the rectum and tenderness, suppression of urine, and collapse. There may be coldness of the skin, hallucinations, and coma. In some instances partial paralysis has occurred, suggesting a neurotoxic phase. Symptoms generally appear within a few hours after ingestion of the poison and last for two or three days. Savage and others believe that most instances of potato poisoning are due not to solanin but instead to bacterial infection.

Favism is a form of poisoning resulting from the ingestion of the *Vicia favia* (fava bean, horse bean, brind bean). A similar clinical picture results from inhaling the dust of the bloom. This form of poisoning is more common in Mediterranean areas where the fava bean is a staple article of diet. Children are particularly susceptible. After ingestion of the bean symptoms appear in twelve hours or more, whereas after inhalation they appear in a few minutes to several hours. There are fever, anemia with jaundice, hemoglobinuria and often pain, nausea, vomiting, and diarrhea. Severe lumbar backache may be distressing. There may be chills. There may be marked eosinophilia. There is a seasonal incidence, being maximum in spring. Besides the existence of a specific poison, allergic sensitivity and plant infestation with bacteria or fungi have all been suspected as being etiologically

involved. The attacks usually last for two to several days. The condition may be confused clinically with "black-water fever."

Oxalic acid is a common constituent occurring in widely varying amounts in sour grass and rhubarb. Soup made from sour grass, a species of sorrel, has produced symptoms resembling staphylococcic food poisoning. The eating of dried rhubarb leaves has proved fatal, the noteworthy symptoms being marked exhaustion, hemoptysis, early cardiac failure, and an increased coagulation time of the blood. It has been believed by many that the "indigestion" attributed to the ingestion of rhubarb has been due to allergic sensitivity rather than to any specific poison such as oxalic acid.

Parasites of Plants.—*Ergot*, according to Webster,[2] is the dried sclerotium of the parasitic fungus *Claviceps purpurea*. It develops on the rye plants and replaces the grain of rye *(Secale cereale)*. It may be found on other grain and some native grasses. Acute poisoning has resulted from eating bread made from infected rye. Chronic poisoning occurs when such bread is eaten repeatedly. Robertson and Ashby have demonstrated a daily intake of 22.85 gr. of ergot a day in some regular consumers of rye bread. These individuals evidence symptoms of chronic rye poisoning.

Acute ergot poisoning,[1, 2] which is more commonly observed in children and the symptoms of which may not appear for several hours, is characterized by vomiting, pains in the abdomen, tingling of the extremities, thirst, weakness, and diarrhea. There may be edema of the face and extremities. The pulse is usually slow and of poor volume. Paresthesia, especially of the hands and feet, followed by twitching and tonic contractions of the muscles, occurs. Other nervous symptoms such as ataxia, epileptiform seizures, and mania have been described. The temperature is usually subnormal and the urine suppressed. Prostration, coma, and death from cardiac or respiratory paralysis occurs.

The chronic forms of ergot poisoning are of two types: (1) spasmodic and (2) gangrenous. Indefinite pains and digestive disturbances are the early symptoms in both forms.

In the spasmodic form, anesthesia of the fingers and toes, then of the extremities occurs, followed by tetanic spasms of the muscles later, and if the patient lives, these are followed by contractures of the extremities. Depression and asthenia are a common result.

In the gangrenous form, in one or more of the extremities, there is acute pain and swelling and discoloration, and the part is cold. A dry gangrene develops, and there is little pain or bleeding as the fingers, toes, even arms, legs, and nose fall off. Gangrene of internal organs and cataracts may occur.

This form of poisoning has been recognized for years.

Parasites of Animals: As is well known, the ova of some of the zooparasites which at times infest man may be found in the meat of fish and animals, or in the food as a contaminant from the stools of rodents, or as ova or larvae on the plant foods which are usually eaten raw. This form of food contamination is well covered in our medical texts and is probably much better understood than many of the other forms of food contamination.

Bacterial Contaminants.—The bacterial contaminants have already been described under Food Poisonings.

In connection with the matter of prophylaxis of food injuries, the remarks of Lt. Col. George H. Koon, V.C., U. S. Army, at a conference in Denver in July, 1937, are very much to the point.

"Practicing physicians and those doctors engaged in public health work can contribute largely to the epidemiologic control of disease by interesting themselves in and lending their efforts to the Federal Meat Inspection Act. Particularly should such activities be removed from the influence of local or state politics." He also pointed out that in the Army, those food products which are routinely inspected for the purpose of detecting conditions which render them unsuitable for food are (1) meat and meat products, (2) poultry and eggs, (3) fish and shellfish, (4) milk and milk products, (5) canned foods, (6) vegetables and fruits. Ordinarily, such food as sugar, cereals, salt, or spices are not inspected for deficiencies which would impair health. He points out that the surgeon of a command is responsible, from an administrative viewpoint, for the health of recruits. When veterinary officers are not available for duty as meat inspectors, the necessary inspections are made by medical officers. In the United States Navy, the medical officer is directly responsible for seeing that all the requirements of proper health protection are fulfilled as regard to the quality and safety in preparation of all foods permitted. The Bureau of Animal Husbandry's stamp, indicating that meats have had federal inspection, is essential, except under very unusual circumstances.

SUMMARY

In Part I the food poisonings due to bacterial action are discussed.

In Part II an attempt has been made to discuss the other forms of food intoxication in order that they might be considered in their proper relation to bacterial food poisoning.

Some of these intoxications have been discussed more in detail because of their public health significance. others because of the complexity of their epidemiologic study or the hidden potentialities for injury to human beings, and others because of the interesting speculations which they permit.

Special emphasis has been placed on the timely warning in regard to the dangers from the chronic absorption of the tiny "chemo-enemies" cited by Hanzlik.

It was believed that a review of present knowledge on the problems of food-borne intoxication and an attempt to orient properly these conditions with some of the food-borne infections was timely in view of the impending problems of national defense.

REFERENCES

General

1. Damon, S. R.: Food Infection and Food Intoxication, Baltimore, 1928, Williams and Wilkins Co.
2. Webster, R. W.: Legal Medicine and Toxicology, Philadelphia, 1930, W. B. Saunders Co.
3. Jordan, E. O.: Food Poisoning and Food Borne Infection, ed. 2, Chicago, 1931, Chicago University Press.
4. Jordan, E. O.: General Bacteriology, ed. 4, Philadelphia, 1914, W. B. Saunders Co.; also ed. 11, 1935.
5. Rosenau, M. J.: Preventive Medicine and Hygiene, ed. 6, New York, 1935, D. Appleton-Century Co., Inc.

Botulism

6. Koser, S. A., and Reiter, D. O.: J. Prev. Med. 39: 499, 1929.
7. Meyer, K. F.: California & West. Med. 44: 385, 1936.
8. Geiger, J. C.: Pub. Health Rep. 52: 765, 1937.

Salmonella

9. Jordan, E. O.: J. Prev. Med. **3**: 279, 1929 (Cutter Lecture, March 28, 1929).
10. Scott, W. M.: Brit. M. J. **2**: 56, 1930.
11. Sacquépée, E., Liégeois, M., and Fricker, J.: Presse méd. **39**: 313, 1931; Abstracted in J.A.M.A. **96**: 1917, 1931.
12. Geiger, J. C., Nelson, Margaret, and Gray, J. P.: Pub. Health. Rep. **46**: 1565, 1931.
13. Kuttner, A. G., and Zepp, H. D.: Bull. Johns Hopkins Hosp. **51**: 373, 1932.
14. London Letter: J.A.M.A. **99**: 1274, 1932.
15. Kuttner, A. G., and Zepp, H. D.: J.A.M.A. **101**: 269, 1933.
16. Bahrenburg, J. H., and Ecker, E. E.: J. Infect. Dis. **60**: 81, 1937.
17. Schiff, Fritz: J.A.M.A. **111**: 2458, 1938.
18. Andrew, D. H., Korff, F. A., and Ewing, C. L.: J.A.M.A. **113**: 2300, 1939.
19. Brown, E. G., Combs, G. R., and Wright, E.: J.A.M.A. **114**: 642, 1940.
20. Holmes, W. H.: Bacillary and Rickettsial Infections, New York, 1940, The Macmillan Co.
21. Lyon, G. M., and Folsom, T. G.: West Virginia M. J. **37**: 249, 1941.
22. Price, A. M.: Personal Communication. West Virginia M. J. To be published.
23. Mosher, W. E., Jr., Wheeler, S. M., Chant, H. L., and Hardy, A. V.: Pub. Health Rep. **56**: 2415, 1941.

Staphylococci

24. Owen, R.: Physician & Surg. **29**: 289, 1907; Reference: Dievdanne, A., translated by Bolduan, C. E.: Bacterial Food Poisoning, New York, 1909, E. B. Treat and Co., p. 59.
25. Barber, M. A.: Philippine J. Sc. (Trop. Med.) **9**: 515, 1914.
26. Scamman, C. L., Lombard, H. L., Beckler, E. A., and Lawson, G. M.: Am. J. Pub. Health **17**: 311, 1927.
27. Dack, G. M., Carny, W. E., Woolpert, Oram, and Wiggers, Hazel: J. Prev. Med. **4**: 167, 1930.
28. Jordan, E. O.: J.A.M.A. **94**: 1648, 1930.
29. Editorial: J.A.M.A. **95**: 36, 1930.
30. Dack, G. M., Jordan, E. O., and Woolpert, Oram: J. Prev. Med. **5**: 151, 1931.
31. Jordan, E. O., and Hall, J. R.: J. Prev. Med. **5**: 383, 1931.
32. Dack, G. M., Woolpert, O., Noble, Isabel, and Halliday, Evelyn G.: J. Prev. Med. **5**: 391, 1931.
33. Jordan, E. O., and McBroom, Josephine: Proc. Soc. Exper. Biol. & Med. **29**: 161, 1931.
34. Jordan, E. O.: J.A.M.A. **97**: 1704, 1931.
35. Editorial: J.A.M.A. **98**: 820, 1932.
36. Jordan, E. O., and Burrows, William: Proc. Soc. Exper. Biol. & Med. **30**: 448, 1933.
37. Woolpert, O. C., and Dack, G. M.: J. Infect. Dis. **52**: 6, 1933.
38. McBurney, R.: J.A.M.A. **100**: 1999, 1933.
39. Borthwick, G. R.: Brit. J. Exper. Path. **14**: 236, 1933.
40. Jordan, E. O., and Burrows, William: J. Infect. Dis. **55**: 363, 1934.
41. Jordan, E. O., and Burrows, William: Am. J. Hyg. **20**: 604, 1934.
42. Stritrar, J., and Jordan, E. O.: J. Infect. Dis. **56**: 1, 1935.
43. Editorial: J.A.M.A. **104**: 1332, 1935.
44. Goforth, J. L.: South. M. J. **28**: 659, 1935.
45. Corpening, A., and Foxhall, Elsie: Am. J. Pub. Health **25**: 938, 1935.
46. Stone, R. V.: Proc. Soc. Exper. Biol. & Med. **33**: 185, 1935.
47. Dack, G. M., Bowman, G. W., and Harger, R. N.: J.A.M.A. **105**: 1598, 1935.
48. Geiger, J. C., Crowley, A. B., and Gray, J. P.: J.A.M.A. **105**: 1980, 1935.
49. Editorial: J.A.M.A. **106**: 1009, 1936.
50. Denison, G. A.: Am. J. Pub. Health **26**: 1168, 1936.
51. Geiger, J. C.: Pub. Health Rep. **52**: 765, 1937.
52. Timmermann, W. A.: Nederl. Tijdschr. v. Geneesk. **81**: 4443, 1937; abstracted in J.A.M.A. **109**: 1590, 1937.
53. Chapman, G. H., Lieb, C. W., and Curcio, Lillian G.: Food Research **2**: 349, 1937.
54. Kupchik, G. J.: J. Infect. Dis. **61**: 320, 1937.
55. Davison, Ellen, Dack, G. M., and Carny, W. E.: J. Infect. Dis. **62**: 219, 1938.
56. Wade, E. M.: U. S. Nav. M. Bull. **36**: 306, 1938.
57. Wilson, R. J.: Canad. Pub. Health J. **29**: 329, 1938.
58. Cogswell, W. F., Kilbourne, B. K., and Kuhns, Edith: Canad. Pub. Health J. **29**: 333, 1938.

59. Dolman, C. E., and Wilson, R. J.: J. Immunol. **35**: 13, 1938.
60. Grubb, T. C.: J. Lab. & Clin. Med. **23**: 1150, 1938.
61. Editorial: J.A.M.A. **111**: 1568, 1938.
62. Thomas, G. E., and Syslo, J. A.: U. S. Nav. M. Bull. **37**: 351, 1939.
63. Geiger, J. C., and Ragan, W. J.: Food Poisoning, California & West. Med. **50**: 28, 1939.
64. Hackler, John: Am. J. Pub. Health **29**: 1247, 1939.
65. Slocum, G. C., and Linden, B. A.: Am. J. Pub. Health **29**: 1326, 1939.
66. Nunheimer, T. D., and Fabian, F. W.: Am. J. Pub. Health **30**: 1040, 1940.
67. Geiger, J. C., and Crowley, A. B.: Am. J. Pub. Health **30**: 1351, 1940.

Shellfish

68. Meyer, K. F., Sommer, H., and Schoenholz, P.: J. Prev. Med. **2**: 365, 1928.
69. Sommer, H., Whedon, W. F., Kofoid, C. A., and Stohler, R.: Arch. Path. **24**: 537, 1937.
70. Sommer, H., and Meyer, K. F.: Paralytic Shellfish Poisoning, Arch. Path. **24**: 560, 1937.
71. Editorial: J.A.M.A. **110**: 443, 1938.

Chemical

72. Hanzlik, P. J.: Scientific Monthly **44**: 435, 1937.
73. Report of Committee on Foods, American Public Health Association: Chemical Contamination of Food, Am. J. Pub. Health **28** (Supp.): 52, 1938.
74. Ecker, A. D., and Kernohan, J. W.: Arch. Neurol. & Psychiat. **45**: 24, 1941.
75. Smith, M. I.: J.A.M.A. **116**: 562, 1941.
76. Fraut, S., and Kleeman, I.: J. A. M. A. **117**: 86, 1941.*

Miscellaneous

77. Patty, F. A.: J. Infect. Dis. **29**: 73, 1921.
78. Robertson, J., and Ashby, H. T.: Brit. M. J. **1**: 302, 1928.
79. Dilling, W. J., and Kelly, R. E.: Brit. M. J. **1**: 540, 1928.
80. McCrae, Thomas, and Ullery, J. C.: J.A.M.A. **101**: 1389, 1933.*
81. Report of Committee on Microbiological Methods of Food Examination of the Food and Nutrition Section, American Public Health Association, Am. J. Pub. Health **28**: 56, 1938.
82. Luisada, A.: Medicine **20**: 145, 1941.*
83. Robinson, P.: Am. J. Dis. Child. **62**: 701, 1941.*

*Reference added after preparation of manuscript.

The Pediatrician and the War

The following is a continuation list of Fellows of the American Academy of Pediatrics on active duty in the military services:

Army

Dr. Louis Appel, Flushing, N. Y. (Captain)
Dr. J. Lewis Blanton, Fairmont, W. Va. (Major)
Dr. Wyman C. C. Cole, Detroit, Mich. (Lieutenant Colonel)
Dr. Arthur J. Cramer, Jr., Buffalo, N. Y. (Captain)
Dr. Clair L. Douglas, Detroit, Mich. (Major)
Dr. Herman W. Farber, Richmond, Va. (Captain)
Dr. A. S. Finkelstein, Newark, N. J. (Captain)
Dr. Arthur Heyman, Newark, N. J. (Major)
Dr. Lewis Webb Hill, Boston, Mass. (Major)
Dr. Frank J. Jacobson, Providence, R. I. (Captain)
Dr. Robert E. Jennings, East Orange, N. J. (Captain)
Dr. Sidney R. Kaliski, San Antonio, Texas (Major)
Dr. Bruce A. Knickerbocker, Dallas, Texas (Major)
Dr. John McKenney Mitchell, Rosemont, Pa. (Major)
Dr. Norman Nixon, Beverly Hills, Calif. (Major)
Dr. Tracy D. Peppers, Greeley, Colo. (Major)
Dr. Harold D. Pyle, South Bend, Ind. (Major)
Dr. Robert Page Rogers, Greenwich, Conn. (Major)
Dr. Carl E. Sibilsky, Peoria, Ill. (Captain)
Dr. J. B. Snow, Oklahoma City, Okla. (Major)
Dr. Irwin P. Sobel, New York, N. Y. (Major)
Dr. Martin L. Stein, Brooklyn, N. Y. (Captain)
Dr. Sam P. Wainwright, Birmingham, Ala. (Major)
Dr. R. E. Williams, Chicago, Ill. (Major)

Navy

Dr. Jack Basman, Charleston, W. Va. (Lieutenant)
Dr. J. M. Bishop, Roanoke, Va. (Lieutenant Commander)
Dr. Carl L. Cohen, Chicago, Ill. (Lieutenant Commander)
Dr. Harold W. Dargeon, New York, N. Y. (Lieutenant Commander)
Dr. Harry F. Dietrich, Beverly Hills, Calif. (Lieutenant)
Dr. Lee E. Farr, Wilmington, Del. (Lieutenant)
Dr. C. Dixon Fowler, Atlanta, Ga. (Lieutenant)
Dr. Douglas D. Martin, Tampa, Fla. (Lieutenant Commander)
Dr. A. Lane Mitchell, Houston, Texas (Lieutenant Commander)
Dr. Joseph F. Raffetto, Asbury Park, N. J. (Lieutenant)
Dr. Morris Steiner, Brooklyn, N. Y. (Lieutenant Commander)
Dr. T. Durland Van Orden, New York, N. Y. (Lieutenant Commander)

Special

Dr. Emanuel B. Brandes, Cincinnati, Ohio (Passed Assistant Surgeon, U. S. Public Health Service)

Dr. Halcuit Moore, Dallas, Texas (Associate Physician, Colon Hospital, Cristobal, Canal Zone)

Dr. Samuel J. Nichamin, Detroit, Mich. (Passed Assistant Surgeon, U. S. Public Health Service)

Dr. David P. Evans, East Orange, N. J., is Lieutenant Commander in the United States Navy instead of the Army, as listed previously.

The Editors will receive additional names of Fellows entering the services for future lists.

American Academy of Pediatrics

Proceedings

REPORT OF THE ANNUAL MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

The annual meeting of Region III of the American Academy of Pediatrics was held at the Hotel Cleveland, Cleveland, Ohio, May 14, 15, and 16, 1942. The registration, which totaled 518, made up as follows:

Academy Members	188
Guests	204
Exhibitors	126
Total	518

Statement of Receipts and Disbursements

Receipts:

Registrations		$2,180.50	
Exhibit Sales	$3,795.00		
Less Return	450.00	3,345.00	
			$5,525.50

Disbursements:

Banquet	927.37	
Luncheons	500.27	
Exhibit Expense	434.75	
Ladies Entertainment	142.82	
Local Committee	4.57	
Officers of Academy	121.78	
Preparation of Program	54.68	
Publicity to Members	492.94	
Registration	58.25	
Scientific Sessions	700.64	
State Chairmen's Luncheon—Boston	44.85	
Cleveland	41.72	
Committee on Arrangements	231.27	
Miscellaneous	51.76	
		3,807.67
Increase		1,717.83

Bank Balance, 7/1/41	2,341.80	
Bank Balance, 7/1/42	2,209.63	
U. S. Treasury Bond	1,850.00	
Total Assets, 7/1/42		4,059.63

ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 9-11, 1941

Round Table Discussion on Orthodontics

Chairman: Alfred Paul Rogers, D.D.S., Clinical Professor of Orthodontics, Harvard School of Dental Medicine, Boston, Mass.

Associates: Allan G. Brodie, Ph.D., D.D.S., Professor and Head of the Department of Orthodontia, University of Illinois, Chicago, Ill.

Charles M. Waldo, D.D.S., Assistant Professor of Orthodontics, Harvard School of Dental Medicine, Boston, Mass.

Secretaries: S. Graham Ross, M.D., Montreal, Que.

Benjamin Hoyer, M.D., Cincinnati, Ohio.

Opening Remarks

Alfred P. Rogers, Boston

I should like to make a brief statement to acquaint you with the present trend of orthodontic thought which underlies our efforts in our search for obscure causes fundamental to the development of dentofacial anomalies. From an etiologic standpoint, the historic development of orthodontics, with the pronounced mechanical inclination of its practitioners, may, in part, be responsible for delayed understanding in these important factors of dentofacial anomalies.

Orthodontists do not think longer of these professional activities as being purely mechanical in nature. We are concerned with the development and function of living machinery, and in that our practice is essentially orthopedic in nature. It is true that a refined mechanics must be employed in the treatment of many dental anomalies. Such mechanical treatment can be looked upon as merely symptom treatment. Being of a corrective nature, it is, of course, extremely important. In recent years we have been looking deeper into the problems of growth and development and have found it necessary to become active students of the basic biologic sciences in seeking a better understanding of the etiologic factors which underlie dentofacial anomalies. In trying to arrive at some decision as to what education is of most worth to the orthodontist, we have reached the conclusion that all fundamental studies which have a bearing on growth and development of the individual are necessary.

You may, therefore, well understand that we welcome discussion with men whose primary interest is the healthful development of mind and body of children, men whose studies we feel we must share when we consider factors underlying growth and development. We would do well to pool our resources and techniques in an integrated series of researches dealing with the many aspects of those developmental factors and welded in a connected and unified effort to restore the inherent ability

Read before American Academy of Pediatrics, Boston, Mass., Oct. 9 and 10, 1941.

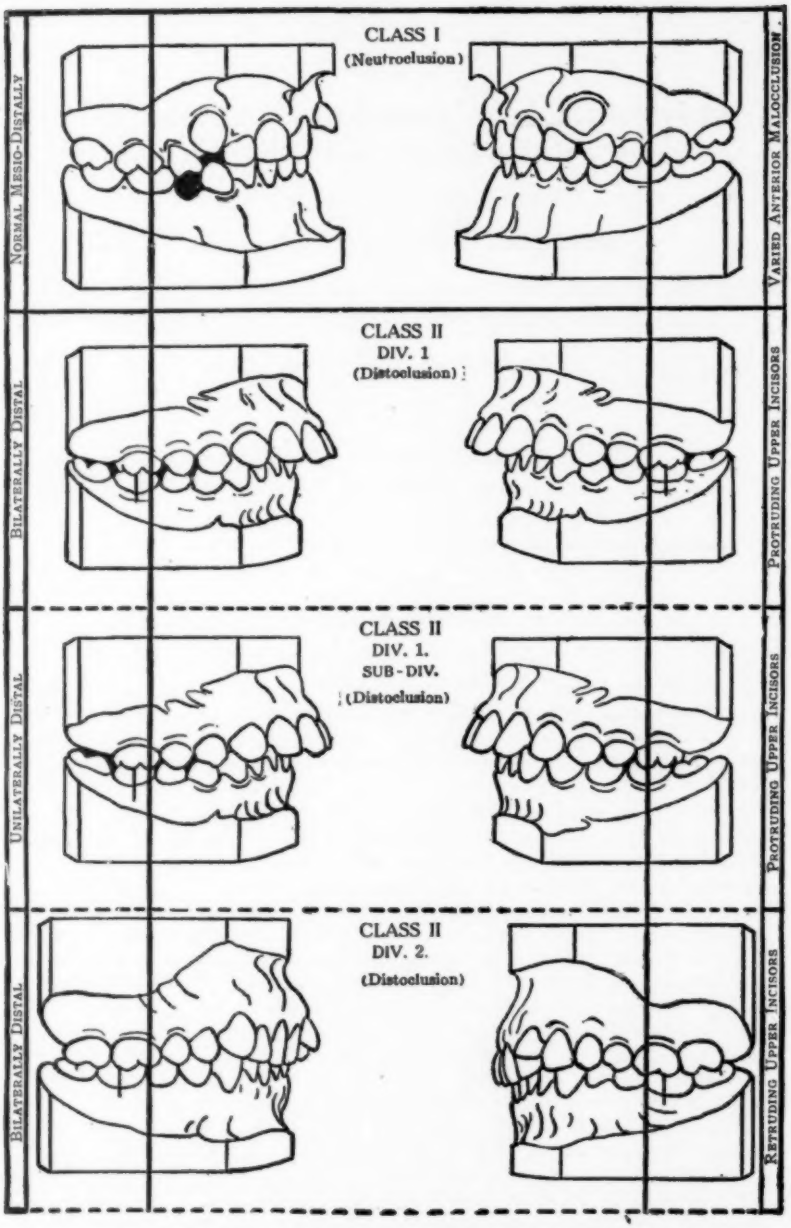


Fig. 1.—Angle classification of malocclusion. (From Johnson's *Operative Dentistry*, The Blakiston Co.)

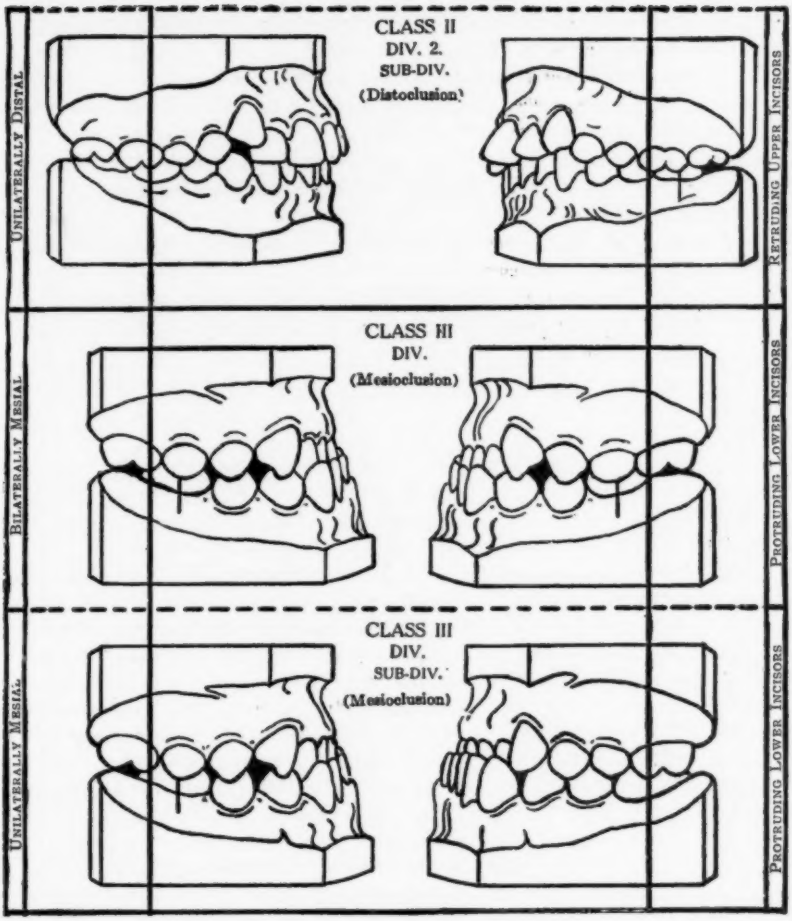


Fig. 1.—Cont'd.

of the organism to attain full maturation. One of our great hopes lies with those who are trained and situated as you are to see children early in life, and thereby recognize the early stage of developing dentofacial anomalies.

In addition to a consideration of the basic problems, it will be necessary on this occasion, in order to make this round table conference complete and immediately beneficial, that we also consider some of the problems relative to daily practice. For example:

1. Cooperation between the pediatrician and the orthodontist.

2. Those complex emotional conflicts between the mother and child in reference to habits having a tendency to promote oral deformities.

3. The influence of mouth breathing over prolonged periods when seen to interfere with the proper development of the dental arches.

4. Treatment that is necessary in cases of partial anodontia.

5. A consideration of the variability of length of time for periodic orthodontics.

6. Jaw deformities due to birth injuries.

7. Subluxation of the mandible in infants (mandibular dysplasia).

8. The relative importance of orthodontic treatment in relation to other necessities of life—an economic problem.

9. Importance of malocclusion to the child, both physically and emotionally.

10. The nervous reactions in childhood due to orthodontic treatment and how best to avoid them.

11. The type of child deemed by pediatricians as too nervous or physically unfit to undergo orthodontic treatment.

12. Differentiate the acquired types from those due ot congenital abnormalities.

13. The age at which the orthodontist should see the patient and what determines the age when treatment should be undertaken.

14. What the pediatrician can do to help the infant and young child before appliances can be adjusted.

15. Malnutrition as a basic factor in dentofacial anomalies.

It is important that pediatricians know something of the classifications of malocclusion when making routine physical examinations, that they may examine the oral cavity upon the basis of accepted definition of the various types of malocclusions. A general understanding of the various types should be sufficient.

Almost fifty years ago Dr. Edward H. Angle interested himself in the study and correction of what at that time were uniformly spoken of as "irregularities" of the teeth. Dr. Angle had succeeded in securing many hundreds of plaster casts of dental anomalies and finally, after much study, completed the first satisfactory classification. His procedure was direct and logical in that he placed in different groups plaster casts which presented like variations from a typical, or so-called normal, occlusion. To state the matter briefly, his efforts resulted in separation into three groups which he classified numerically as Class I, Class II, and Class III. Then, from a further study into the characteristics of each of these classes, he found less obvious departures from the normal. These he designated as subdivisions.

The Nature of the Orthodontic Problem

Allan G. Brodie, Chicago

The dental apparatus of man, like other parts of his economy, comes to a full normal maturity only as a result of the normal operation of hereditary, congenital, and environmental factors. Until recently the conscientious orthodontist has been paying strict attention to environmental factors only because so little was known of the first two that recourse to them, as a reason for failure or an explanation of cause, smacked of evasion. The research work in the basic sciences, particularly of the past decade, has caused him to re-examine his groundwork and has made him more sensitive to biologic processes at the same time that it was deflating his ego. While the book on heredity has still to be written, work in experimental embryology and investigations on human growth have thrown light on many problems that were formerly "blind spots."

Experimental embryology, employing irritants and transplants, have proved beyond any reasonable doubt that the form of bones is genetically determined. Small collections of cells removed from the anlage of a hind limb and transplanted to a strange but favorable environment will give rise to an easily defined femur.

But this is not all. Weiss, in his *Principles of Development*, recounts innumerable experiments which prove that in its earliest stages the surface of the embryo is composed of a series of fields, each competing with the others for nourishment. The organization of such a field is characterized by the presence of a focal point at its center where potency is highest. From this point the potency diminishes as the periphery is approached. Transplants from such a center will give rise, in the host, to the formation of the organ for which it was specializing in the donor; whereas tissue removed from the periphery of the field will be incorporated into the tissue or organ of the host to which it is carried.

But more important from our standpoint is the discovery, or realization perhaps, that growth centers do not appear simultaneously but in an orderly sequence that covers a long period of time. Very little is known at the present in regard to either the time or sequence, except in the case of the teeth and some of the bones. The close study of the former by Schour and his co-workers, however, has yielded certain findings that are of equal importance and may, indeed, furnish the key to this problem. Briefly, these findings are as follows:

Growth centers exhibit their highest rate of activity at the instant of their appearance and gradually diminish as the age of their cells advances. Probably no two centers have the same rate and gradient. Nor do all centers have the same span of development. These differences in time, rate, and locus operate to transform the embryo from a disclike structure into the easily recognized fetus of three months. This largely completes the phase of disproportionate growth or morphogenesis. Body form has been established and development from there on is a matter of varying rates of appositional growth. Such rates, however, are so integrated that changes in proportion are held to a minimum.

Scammon and Calkins, in a study of a large mass of fetal material, referred various body dimensions to the crown-heel length as a norm and obtained a series of straight lines representing the various ratios. Their conclusion from this was that growth of the body was strictly proportional from the third month on. The author, working on living children from the third month to the eighth year of postnatal life, found exactly the same type of growth.

Serial cephalometric roentgenograms taken according to the Broadbent-Bolton technique yield an accurate, progressive record of the head of the same child over the entire growth period. Such records have been gathered on hundreds of children over the past fourteen years. The superimposing of tracings from such x-rays gives a striking picture of orderly progress from birth to maturity. If one represents with straight lines such structures as the floor of the anterior cranial fossa, the floor of the nose, the occlusal plane of the teeth, lower border of the mandible, etc., it is found that they bear constant angular relations to each other and that the series of lines representing any stage of growth will be parallel to the same series of any other period. Furthermore, the distances between the lines at any plane maintain the same proportions. Strangely enough, the deformed head exhibits the same orderly progress and the same stability of relations. One can only conclude that the incremental growth is proceeding normally but on a pattern that has been distorted during the stage of morphogenesis.

The investigations on the development and growth of teeth have furnished us with an explanation of these findings. Growth centers in the teeth, like those in the bony skeleton, appear at different times. Furthermore, their incremental growth proceeds at different rates. Since the time of appearance of centers has been adequately studied, it is now possible to date the onset of a disturbing factor by noting

the teeth that are affected. Thus, markings on the tips of the cusps of the first permanent molars indicate a disturbance at birth or shortly after. Edges of central incisors and tips of canines reflect adverse factors operating during the first three postnatal months. The lateral incisors do not begin to form until approximately the first year and hence would not be affected by factors operating before that time. The important point to be made here is that only those centers that are active at the time of operation of the disturbance are affected. These are distorted or arrested, but those that appear later are not influenced in any way. When recovery occurs, growth proceeds in a perfectly normal manner, albeit perhaps on a distorted pattern, but the working time that has been lost by the cells is never made up. Sarnat has recently pointed out that this probably explains why only central incisors and first permanent molars exhibit the Hutchinson pattern of early congenital syphilis.

Now if we transfer these principles from a system of independent growth units, like the teeth, to a system of interdependent parts, such as the skeleton of the cranium and face, we have a logical explanation of the occurrence of congenital deformities and of their growth. Thus, a factor that operates before all of the growth centers are working will affect only those that are active at the time. In such a case, centers appearing subsequently and after recovery will fulfill their potential of growth and thus be out of proportion to the arrested parts. It thus becomes evident that the *time* of occurrence rather than the nature of a disturbing element is the determinant.

Our major problem at present is to work out the order or sequence of appearance of growth centers. This would give us important information on relationships. This work is already partly accomplished. We then want to place this sequence table against chronologic age. With these two sets of data at our disposal it would be possible to date the time of occurrence of a cranial or facial deformity with the same or greater accuracy that we can now date disturbances affecting the teeth.

In a general way we may say that disturbances in cranial growth, and particularly of the anterior portion of the base, are very early. Since this area is the foundation upon which the upper face is reared, we would expect associated distortions here, particularly in the upper nasal area. Posterior cranial growth and the growth of the entire face may be affected beginning at birth, as in some forms of cretinism. The cretin, in fact, furnishes us with some very conclusive data on our problem. At birth the infant may be normal in development, but upon being shut off from the hormone of the mother suffers a uniform, and almost complete, retardation of growth. Obviously, those parts that are closest to their full development, like the anterior cranial fossa, will suffer least, while those parts that still have considerable growth expectancy will suffer the most. Untreated, the cretin remains infantile in pattern; treated, he presents a picture that will tell how long his deficiency lasted.

Factors influencing the mandible would occur at a relatively late date, and the growth center at the condyle of this bone is particularly vulnerable to localized environmental disturbances. Extreme deformity follows the resection of the condyles in cases of ankylosis if the operation is performed during the growth period. The resulting deformity is identical in pattern to that of the well-known micromandibular type, or "Vogelgesicht" of European literature.

And finally we come to the most frequently occurring deformity found in modern man; that is, malocclusion of the teeth. On the basis of what has been said, this high incidence in one particular area might seem contradictory were it not for the fact that we are dealing with dissimilar structures. The teeth are laid down at a

relatively early date in postnatal life and are not subject to any subsequent alteration. The jaw bones which are to hold them, however, do not fulfill their growth before the eighteenth to the twentieth year. Furthermore, the precise nature of the relationships that must exist between teeth if they are to occlude normally magnifies any discrepancy between teeth and jaws to far beyond the significance it would have elsewhere. A man whose legs have failed by an inch to attain their full length goes unnoticed, but one whose jaws fail by an eighth of an inch is a dental monstrosity.

From what has been said it should be apparent that the orthodontic problem embraces more than thumbsucking, sleeping on the fist, or breathing through the mouth. While these factors are very influential in altering the form of the occlusion of the teeth, they do not constitute more than a fraction of the etiologic factors with which we must reckon. Eliminating all consideration of hereditary influences, about which we are in almost total ignorance, we are faced with the challenge of preventing congenital mishaps and of keeping children well during their growing period. This means a striving for perfect health of the mother during pregnancy, an uneventful neonatal period, and a healthy, robust childhood. These latter problems the orthodontist must leave to the pediatrician.

REFERENCES

Brodie, A. G.: Am. J. Anat. **68**: 1941; Am. J. Orth. & Oral Surg. **27**: 633, 1941.
Engel, M. B., Bronstein, I. P., Brodie, A. G., and Wesoke, P.: Am. J. Dis. Child. **61**: 1193-1214, 1941.
Fell, H. B., and Robison, R.: Biochem. J. **23**: 767-784, 1929.
Sarnat, B. G., Schour, I., and Heupel, R.: J. A. M. A. **116**: 2745-2747, 1941.
Scammon, R. E., and Calkens, C. A.: The Development and Growth of the External Dimensions of the Human Body in the Fetal Period, Minneapolis, 1929, University of Minnesota Press.
Schour, I., and Massler, M.: J. A. D. A. **27**: 1778-1793, 1918-1931, 1940.
Weiss, Paul: Principles of Development, New York, 1939, Henry Holt & Co., Inc.

Synopsis of Orthodontic Problems

Charles M. Waldo, Boston

It is the purpose of this discussion to touch briefly upon the nature of some of our problems and to point out the way in which some aspects of recent research bear upon them.

It is safe to say that our real problems are not those of mechanical treatment but are rather those incident to the decisions which must be made before treatment is started or even planned. For example, they are those which arise when we examine a particular patient and ask ourselves: Is anything wrong with this patient? What is it? Does he need treatment? Obviously these are questions which must be answered in some way by every clinician in every patient he sees, and the answers to all must depend upon the clinician's idea of what is right. This basic concept of what is right or "normal" will largely determine other concepts fundamental to the whole structure of clinical practice.

As Dr. Rogers pointed out, the concept of "normal" as a fixed, clear-cut ideal is an excellent basis for classification of malocclusion. It is extremely useful for purposes of description but it does not materially help us to decide for a particular patient (1) what conditions constitute a departure from health, (2) what constitute a danger to future health, and (3) what is needed to maintain or restore that desirable state.

During the last decade or so a number of research groups have focused their attention on the individual human organism. They have pointed out repeatedly: (1)

that individuals differ in almost every attribute and characteristic studied, that the range of such variation is often wide and, what is most important, that even wide variations may be entirely consistent with health; (2) That repeated examinations of the same individual, particularly if he is growing, aid greatly in determining how he differs from other individuals, what his inherent patterns, trends, and tendencies may be, and what should be considered "normal" for him. (3) that genetic factors and potentialities undoubtedly play an important role in determining not only what an individual is but how he reacts to his environment; (4) that consideration of the whole individual organism is necessary in evaluating either health or a departure from it.

Applied to orthodontics, all of these call for a broad concept of "normal" and indicate that the best standard we can use is the health of the patient; that our job consists in helping each patient to make a healthy, happy adjustment to his own particular environment. In other words, our real concern is not so much in giving each patient a perfect denture as in giving him one that will neither interfere with his physical well-being nor worry him because of his appearance.

This logically focuses attention upon those conditions, within our province, which handicap the patient in making a satisfactory adjustment to his environment. Our efforts are likely to be directed toward deciding whether or not such handicaps exist (or threaten to exist in the future) and the steps to be taken to prevent, modify, or remove them.

Just where to draw the line in deciding whether any set of conditions is of such severity as to indicate treatment is a question which will always depend upon clinical judgment. An arrangement of the teeth which might seriously affect the physical well-being of one patient might be well tolerated by another whose general health is better or whose will to overcome handicaps is greater. Obviously, a consideration of the whole individual organism (including his environment) is essential.

For purposes of illustration, handicaps (of orthodontic interest) might be grouped as follows:

A. Handicaps to physical well-being.

1. Conditions which seriously interfere with the mastication of food. Examples: deformities in which only a few teeth come into occlusion and those in which opposing teeth interlock in such a way as seriously to limit function.

2. Conditions which endanger the health of the teeth themselves, their supporting structures, or the soft tissues adjacent to them. Examples: deep overbites in which the lower incisor teeth bite directly on the tissues of the palate and those in which malalignment or interlocking of teeth subject them to severe unnatural stresses and strains.

3. Conditions in which the mechanical relation of the opposing teeth tends to restrict or pervert facial growth. Examples: cases in which all the lower teeth bite entirely inside the upper teeth, tending to exaggerate the width of the upper arch and restrict that of the lower, and those in which lower incisor teeth bite outside of or in front of the upper incisor teeth.

B. Handicaps to mental well-being. These cannot be as readily defined or illustrated since they depend to a great extent upon the patient's personality, mental balance, and background of experience. It might be helpful to group them as follows:

1. Handicaps in which dental factors are predominant. (These would consist of definite deformities which obviously detract from the patient's appearance.)

2. Handicaps in which psychologic factors are predominant. (These would consist of minor deformities or irregularities which are of concern to the patient himself but do not obviously detract from his appearance.)

Combined with an aggressive personality and a satisfactory adjustment to environment, even a severe deformity may not constitute a handicap. On the other hand, the importance of a trivial irregularity should not be underestimated if it is a source of worry to a timid, insecure person. His problem should be considered with reference to general health and, in the second group especially, the possibility of eliminating the patient's concern without resorting to orthodontic treatment should always be considered.

Combined with a concept of "normal" bearing a functional relation to the patient, there is an obvious need for a much more intimate and extensive knowledge of both patient and environment than we have used heretofore. The value of repeated examinations as a means of obtaining this information has been strongly emphasized by research and their importance in connection with the foregoing is evident. Observation is not new in orthodontics, but the indications are that it should play a much more prominent role in our practices than it has heretofore, and that it should be broader in scope, including a consideration of factors rightly belonging to orthodontics, medicine, genetics, anthropology, psychology, and sociology. In borderline cases, especially where there is no evident impairment of health, a period of observation and study often covering several years is indicated before treatment can be undertaken on a sound basis. It is common clinical experience that first impressions may be strongly modified or changed as a result of observation, and it should be emphasized that an intimate acquaintance with the patient may be as important as specific dental knowledge gained in deciding whether or not to treat.

This discussion is admittedly fragmentary and, while it will not help materially in giving satisfactory answers to the questions you may ask, it may serve to indicate the nature of our problems and our approach to them and to point out why it is difficult to formulate general rules. The answer to our questions as well as yours must depend upon a knowledge of the particular patient, his needs, his biologic assets and liabilities, and a careful weighing of values.

DISCUSSION

DR. H. CHANDLER CLARKE, NEW ROCHELLE, N. Y.—Does giving of cod-liver oil in pregnancy affect calcification of the deciduous and permanent teeth? If so, what is the optimum dose and is a concentrate preferable? How long in years should cod-liver oil be given to affect the temporary and permanent teeth?

DR. BRODIE.—Yes, the deciduous teeth have begun to grow, although usually are not erupted at birth. Calcification of permanent teeth is affected more by cod-liver oil given after birth. This is usually completed by the eighth year.

DR. CLARKE.—At what age does the dentist stop thumb-sucking?

DR. WALDO.—The habit is not so important during the first few years. If it persists after the age of three or four, special attention should be given to it. Direction of the child's attention to other activities, removal of sources of irritation, and evidence of fatigue and excitement are important. Mechanical restraints are not desirable but may be necessary if other means are not successful.

DR. L. SNEDEKER, BOSTON.—Does eruption of teeth cause thumb sucking?

CHAIRMAN ROGERS.—It may be a contributing factor, but the habit usually starts before this time. It is better for the dentist or physician than the parents

to direct correction of the habit. Tongue-biting and lip-sucking are often substituted when the thumb-sucking habit is broken. Such habits are very persistent and require careful correction.

DR. WALDO.—The effort at correction of habits should be definite and direct, not haphazard.

DR. J. B. AHOUSE, YONKERS, N. Y.—I have a patient 4 years of age with closely set teeth but with otherwise good occlusion. One dentist advised extraction of some of the teeth. Should this be done?

DR. WALDO.—No, there is reason to believe that the jaws will grow.

DR. E. S. GOODWIN, ALBANY, N. Y.—For wide spacing of teeth should soft tissue be removed?

CHAIRMAN ROGERS.—This is a controversial question. It is better to be conservative unless bone is interposed, in which case it should be removed. In my experience about 75 per cent prove to be self-correcting.

DR. BRODIE.—Excess spacing between central incisors gradually closes as lateral and canine teeth erupt.

DR. R. E. NUTTING, DULUTH, MINN.—What is the effect of orthodontics on the hard palate and nasal space?

DR. BRODIE.—There is no effect on the hard palate or nasal space. The effect does not go beyond the bone surrounding the roots of the teeth involved.

DR. ENID C. BROWN, BUFFALO, N. Y.—If, at the age of 10 months, there is malocclusion between the lateral and central incisors, the lateral coming behind the centrals, what treatment is indicated?

DR. WALDO.—Leave them alone.

DR. CLARKE.—How can stains be removed from teeth?

DR. BRODIE.—If staining material such as iron salts are taken up by the teeth directly from the saliva, there is no way of removing such stains.

DR. P. J. McGUIRE, HOMESTEAD, PA.—Is there much danger from iron ammonium citrate ordinarily given in the milk or in other ways?

DR. BRODIE.—If such preparations in very concentrated form come in direct contact with the teeth, they will be stained. Such feeding should be done by tube and followed by thorough rinsing of the mouth.

DR. CLARKE.—One of a pair of twins for whom I am caring cannot suck; that is, he cannot close his jaws. There is a space of increased density in the x-ray of the jaw in this case. What is the cause of this?

DR. BRODIE.—One should look for the lack of muscular control, unless bony ankylosis can be demonstrated.

CHAIRMAN ROGERS.—Subluxation of the mandible sometimes is present at birth. Cross-bite is another type of deformity due to minor birth trauma.

DR. BRODIE.—Too much attention is given to subluxation. The range of movement is great. Apparent subluxation may be overcome as growth takes place. One type of difficulty, in which the child regurgitates food, is due to a relatively oversized tongue, not to underdeveloped mandible.

DR. H. P. FINE, PERTH AMBOY, N. J.—What would you recommend for congenital hypoplasia of the mandible?

CHAIRMAN ROGERS.—In one case about which I was consulted (recently reported in THE JOURNAL OF PEDIATRICS) a cloth helmet, of skullcap variety, with attachments was made to serve as a support for the mandible. This apparatus appeared to be quite effective.

DR. FINE.—To whom should the patient needing orthodontic treatment be referred, to the general dentist first or to the orthodontist directly?

CHAIRMAN ROGERS.—You should be governed concerning this as you would in referring a patient to a specialist such as the orthopedic surgeon or the pediatrician, according to conditions present. There is still a great lack of appreciation of orthodontics by general dentists.

DR. E. J. LAMB, SANTA BARBARA, CALIF.—I enjoyed Dr. Brodie's work since it helps to answer some questions asked by parents. The child should be considered as a whole, including his family and race. Where there is an orthodontic problem, the ossification centers should be studied, especially those in the skull. This may lead to endocrine therapy. Mechanical factors, such as lying on the hand, or having the bottle too long, play a part in the production of deformities of the jaws. Greater success can be obtained by closer cooperation between the orthodontist and the pediatrician.

DR. J. V. GREENEBAUM, CINCINNATI, O.—Dr. Brodie, if, as you show, that at 2 years of age the teeth are fixed in the jaw, not being subject to any subsequent alteration, and the jaws continue to grow until the eighteenth to the twentieth year, will attempted orthodontic treatment tend to throw this relationship out of line in an unfavorable manner?

DR. BRODIE.—No, if the correction is made early it may prove beneficial. The longer correction is put off the less apt you are to get improvement. However, early jaw deformity frequently cannot be recognized except by x-ray.

DR. GREENEBAUM.—It was interesting to hear the discussion about the effect of prenatal diet on the development of the teeth in the offspring. In Cincinnati, Dr. T. K. Selkirk, Dr. A. Graeme Mitchell, and I studied the effect of diet during pregnancy on the offspring for such conditions as rickets, the development of the teeth, the nutrition, the bony development, and the like. These observations on the same children were presented before the American Medical Association and the American Dental Association in 1926 and 1930, respectively. We were astonished at the time to note the splendid condition of the teeth and the dental arches in this group of children who were chiefly of the colored race. Even though there were varying degrees of rickets present in infancy, none of these children later in life needed any orthodontic treatment.

DR. WALDO.—Both of these seem to be common findings; i.e., lack of positive correlation between rickets and malocclusion, and a low incidence of malocclusion in Negroes. The latter may be due both to strongly expressed racial characteristics and to a relatively pure racial background.

DR. BRODIE.—We have made the same observation on numerous colored children. However, it should be pointed out that the incidence of malocclusion is lower in the colored race than in the white.

DR. F. W. BUSH, ROCHESTER, N. Y.—Where teeth have been knocked out, how early can space retainers be used?

DR. BRODIE.—It depends upon the area involved. Ordinarily no space maintainers are necessary in the upper incisor areas, which are usually the site of the injury.

QUESTION.—What do you think of advertisements advising chewing gum for children.

DR. BRODIE.—Chewing gum is apt to make the deformity worse if this is on a local basis.

CHAIRMAN ROGERS.—Gum chewing is undesirable for children suffering from certain types of malocclusion, as Dr. Brodie has explained. When practiced during certain periods of development, it may tend to exaggerate the tendency toward distoclusion. In children wearing delicately adjusted apparatus, it may sometimes interfere with the appliances by bending or loosening the attachments.

DR. MARJORIE F. MURRAY, COOPERSTOWN, N. Y.—At what age should orthodontic treatment be started?

DR. BRODIE.—There is no definite age. It vareis with the individual and the type of case, anywhere from 2 to 45 years.

DR. LAMB.—Will some appliance behind the teeth stop the habit of the protruding tongue?

CHAIRMAN ROGERS.—It will, but I believe that a more helpful way is by teaching the child constructive tongue exercises.

QUESTION.—Is it not true that it is becoming the custom to postpone correction and to shorten the length of time that appliances are used?

CHAIRMAN ROGERS.—Yes, in answer to your second question, we do try to shorten the time that we use appliances, but the correction of the abnormal condition should begin as soon as constructive work can be started.

DR. HOYER.—It has occurred to me that some orthodontic problems might be avoided or corrected by the proper use of the muscles of the face, such as correcting faulty habits of chewing and mastication, and teaching the proper use of the tongue and lips in overcoming faulty or lazy habits of speech. Can something be done along this line?

CHAIRMAN ROGERS.—There is much that can be done by establishing the correct use of facial muscles. Coordination of the various muscle groups is quite as essential as their increased strength. There are certain types of malocclusion which may be prevented by the employment of exercises of the appropriate groups of muscles. In a word, normal function of the muscles of the face tends toward general satisfactory development of the dental apparatus.

QUESTION.—What is the frequency of orthodontic defects?

DR. BRODIE.—There are no satisfactory statistics on this question, largely because malocclusions vary to such a degree that investigators cannot agree on what constitutes a real defect. I think it would be safe to say 50 per cent of the white population are afflicted.

CHAIRMAN ROGERS.—If we include slight malocclusion, the frequency of orthodontic defects would, of course, be very high. I should think more than 70 per cent would show these defects. However, we would find a very small percentage when we consider dental deformities that would classify children as dental cripples.

DR. A. W. WYCKOFF, CLEVELAND.—What should be done with persistent deciduous teeth?

DR. BRODIE.—Leave them alone unless cavities or ankyloses are present. In considering the eruption of teeth, the physiologic rather than the chronologic age is important.

DR. CLARKE.—How should supernumerary teeth be handled?

DR. WALDO.—Removal without damage to other teeth. Simetimes when adjacent teeth are congenitally absent, supernumerary teeth may be utilized. This possibility should be considered before their removal.

DR. H. F. DIETRICH, BEVERLY HILLS, CALIF.—Should deciduous teeth be removed if they persist after eruption of permanent teeth?

DR. BRODIE.—They should be removed.

DR. LAMB.—Some orthodontists advise removal of sound teeth to aid in orthodontics, and the pediatrician is asked for advice.

DR. WALDO.—The removal of sound teeth can be used as a very definite aid in the treatment of some types of malocclusion, but it should always be part of a carefully thought-out program and should be used with caution. In the treatment of malocclusion, this is often one of the most difficult decisions to make and one most likely to depend upon the individual nature of the case at hand. An opinion which considered the competence and judgment of the orthodontist in question would seem to be the best advice the pediatrician could give in most of these cases.

DR. BEN BENJAMIN, MONTREAL, QUE.—If deciduous teeth are so carious that they must be extracted, are there indications which call for orthodontic treatment to prevent drifting?

CHAIRMAN ROGERS.—Large spaces should be filled to prevent drifting.

DR. NICHOLS.—Should a tooth be removed for a gum boil? Do gum boils affect general health?

DR. BUSH.—From the standpoint of orthodontics, should teeth with abscesses be removed? Especially, a six-year molar with a superficial abscess.

CHAIRMAN ROGERS.—Remove such foci. The general health may be affected.

DR. R. McINTOSH, NEW YORK.—I have never seen any ill effect from absorption of pus around deciduous teeth. Aside from the possible systemic effect of absorption, is there any ill effect upon the permanent teeth?

DR. LOSCH.—Not in my experience.

CHAIRMAN ROGERS.—Conditions, such as deciduous teeth which have become abscessed or teeth where pus is found around the absorbing deciduous roots, should be remedied as soon as possible in order that the child's mouth may be maintained in a healthy state. I do not remember seeing any ill effects upon the permanent unerupted teeth. The possibility of systemic effects always gives me concern.

News and Notes

The following is the Spring schedule of examinations of the American Board of Pediatrics:

Written Examination:

For all candidates expecting to take the oral examination in the Spring—Feb. 12, 1943, to be held locally under a Monitor.

Oral Examinations:

March 27 and 28, 1943, St. Louis, Mo. (Closing date for enrollment for this examination, Dec. 1, 1942.)

April 24 and 25, 1943, New York City, N. Y. (Closing date for enrollment for this examination, Jan. 1, 1943.)

At the Annual Meeting of the Society for Pediatric Research, Skytop Lodge, Skytop, Pa., April 29, 1942, the following officers were elected:

President: Dr. Joseph A. Johnson, Henry Ford Hospital, Detroit, Mich.

Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia, Pa.

The recent questionnaire to Fellows of the Academy asking for an opinion on an emblem for personal use resulted in a vote of

No	411	
Yes	180	
Yes-No	89	("Yes" to first question, "No" to second)
Total	680	

The Children's Bureau together with the Women's Bureau of the Department of Labor has recently issued a brief bulletin outlining standards for maternity care for the employment of mothers in industry. It emphasizes the necessity of avoiding night work and the need of rest for pregnant women, with a limitation of hours of employment and the avoidance of any employment where heavy work is necessary or work with exposure to certain toxic substances.

It recommends a six-week leave of absence before delivery and a two-month leave of absence after delivery without loss of employment.

Dr. George S. Frauenberger, who has been Director of Clinics at the Children's Hospital at Philadelphia, has been appointed Chief of the Division for Handicapped Children in the Bureau of Hygiene and Health Department of New York City.

Dr. H. Chandler Elliott, Department of Anatomy, University of Toronto, is in need of material for a research study on poliomyelitis under a grant from the United States Research Council. Dr. Elliott wishes to obtain complete spinal cords

in acute cases of poliomyelitis in patients who had died from the disease itself, and from chronic cases of poliomyelitis in patients dying from other causes some time after the paralysis. The requirements are as follows: "Intact cords, or intact upper or lower halves; dura left on, but slit up the back; cord may be cut into equal halves or thirds for convenience. Fixation preferably with 2 per cent glacial acetic acid in 95 per cent alcohol, but may be formalin in normal saline; use about a pint; please fix straight. If sections are required for local records, I prefer to prepare them myself—if donor removes blocks for this purpose, it impairs value of the material. Correspondence is cordially invited."

Dr. Hattie E. Alexander of Columbia University will deliver the eleventh annual series of the Benjamin Knox Rachford Lectureships on Thursday evening, November 12, and on Friday evening, November 13, at 8:15 P.M., in the auditorium of the Children's Hospital Clinic and Research Building. The subjects of her lectures will be "Experimental Basis for Treatment of Hemophilus Influenzae Infections" and "Treatment of Hemophilus Influenzae Infections and of Pneumococcus and Meningococcus Meningitis."

Book Reviews

The Pharmacopoeia of the United States of America. Twelfth Revision (U.S.P. XII), Philadelphia, 1942, United States Pharmacopoeial Convention, Inc., 880 pages. Price not given.

The twelfth revision of the Pharmacopoeia of the United States of America (U.S.P. XII) has been prepared by the Committee of Revision for 1940-1950, E. Fullerton Cook, Ph.D., Chairman. The complexity and rapidity of medical development have resulted in a thorough revision of this standard reference work. Certain basic policies apply today with as great force as when they were first established. There is a long list of added items and many deletions. Through the use of supplements, further changes will be indicated at intervals and when needed. While the days of "shotgun" remedies may be safely waning, there is still need for a standard yardstick and authority for proper therapeutic agents and a still greater need for frequent reference to such authority.

McCULLOCH.

Chinese Lessons to Western Medicine. A Contribution to Geographical Medicine From the Clinics of Peiping Union Medical College. I. Snapper, Professor and Head of the Department of Medicine, Peiping Union Medical College, Peiping, China, New York, 1941, Interscience Publishers, Inc., 380 pages, 132 illustrations.

Aside from the fact that the title of this book is somewhat misleading, the volume is a significant and interesting account of disease as observed in the Orient in the light of Western Medicine. It makes interesting reading largely because of the informal style of presentation of the material. The study of the application of methods of Western Medicine to the advanced types of cases observed, many of which cannot be seen in other parts of the world, leads to the development of theses of importance and value to be brought back to use in Western Medicine.

The Introduction, which describes the medical clinic of the Peiping Union Medical College, is a fitting tribute to the predecessors of Dr. Snapper in North China, who established and built up the organization in the Department of Medicine of the Peiping Union Medical College. The organization is quite similar to that in certain American medical schools from which much has obviously been copied.

Particularly of value to American readers will be the chapters on nutritional problems and avitaminoses. In view of the widespread interest here in subclinical vitamin deficiencies, the clear-cut descriptions of the forms of deficiency encountered with much regularity in North China should be enlightening. Furthermore, a view is offered of the great influence that nutritional problems may have upon the welfare of society, since much of the incidence of disease in China is due to the inadequate general diet of the populace, the widespread poverty, and the lack of sanitation.

To members of the armed forces who may anticipate service in the Orient, the sections on typhus, relapsing fever, bacillary dysentery, enterocolitis, cholera, kala azar, amebiasis, and amebic liver abscess should prove of interest.

Perhaps the infrequency of arteriosclerosis among the Chinese and the relatively low blood pressure values of normal individuals should be studied by those interested in cardiovascular disease to seek clues to explain the situation in the Western

world. For those who are interested in renal disorders, it is to be noted that skin infections, not acute throat infections or scarlet fever, appear to be the most frequent cause of acute nephritis. Also, the relationship of malaria to a nephrotic condition is worthy of note. The frequency of avitaminosis A, which is one of the most common disorders encountered in North China, and the infrequency of renal stones would indicate that the causal relationship implied by a number of investigators is not borne out in a country where vitamin A deficiency is particularly common. Liver disease was of common occurrence, catarrhal jaundice, liver degeneration and cirrhosis, as well as parasitic diseases such as hydatid cyst, yet gallstones were relatively rare.

Anemia was prevalent and was influenced strikingly by the dietary problems of the populace. Lack of iron-containing foods and the frequency of bacillary dysentery may play a role in the production of the anemias.

One flaw in this monograph, which may be overlooked in the light of the informal character of the manuscript, is the tendency periodically to introduce rather lengthy discussions of unestablished theories of the pathogenesis and etiology of disease processes. Rather than being a formal presentation of the incidence and course of various types of disease encountered in North China, the monograph is a running discourse upon the interesting features of the disorders studied by American methods as impressed upon a Western clinician with a European background.

In general, the book is well written, well printed in readable type with numerous illustrations.

McKHANN.

Psychotherapy With Children. Frederick H. Allen, M.D., New York, 1942, W. W. Morton & Co., Inc., 311 pages. Price, $3.50.

Here is a valuable book written by an outstanding authority on pediatric psychiatry. As Director of the Philadelphia Child Guidance Clinic, Frederick Allen has had an opportunity to study the behavior of children and to help parents with the rearing of their children.

The author follows the viewpoint of the Psychobiological School; he pictures the child as a whole, growing up and making an adjustment in the world. What is more important, he emphasizes growth and development and therefore accepts what might be called the pediatric concept of the problem. Instead of seeing the child as something that can be changed to meet preconceived standards and norms, the writer recognizes him as an individual with the capacity to grow and change. He states, "The principles of therapy stem from an understanding of human growth and change"; and later, "A teacher cannot teach a child a thing unless the child takes part in the learning process."

Throughout the book, case histories are used to illustrate the point which is being made. And in every case the emphasis is on allowing the child to work out his problem. Determination on the part of parents, teachers, and others to help him too often hinders the youngster. The value of therapy is in skillfully using available material so that the child can give vent to his feelings.

This book was written principally for those who do psychotherapy. While describing normal emotional growth and development, it devotes itself largely to the type of behavior problems that are taken to the psychiatrist. Although the nomenclature is not difficult, a part of the subject matter is not easily grasped by those who have not interested themselves in psychiatry. There is in the book, however, a great deal of information which would interest and help the pediatrician in his general practice.

BEVERLY.